Two-Year Safety and Tolerability Study of Enfuvertide Use in Salvage Therapy of Thai HIV-1 Experienced Cases

Wisit Prasithsirikul MD*, Mattana Hanvanich MD**,
Surapol Suwanagool MD***, Winai Ratanasuwan MD***,
Thanomsak Anekthananon MD***, Wichai Techasathit MD***,
Khuanchai Supparatpinyo MD****, Asda Viphagool MD*****

** Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, Thailand*
*** Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*
**** Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
***** Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*
****** Bamrungrad International Hospital, Bangkok, Thailand*

Objective: *To assess safety and tolerability of enfuvirtide, an antiretroviral, in Thai patients with advanced HIV-1 disease who have received antiretroviral treatment and failed on regimens that contain at least one of each antiretroviral (ARV) classes (PIs, NRTIs, and NNRTIs), or who have intolerance to previous antiretroviral regimens.*
Material and Method: *An open-label non-comparative study of enfuvirtide used in salvage regimens along with the backbone antiretroviral therapy of choice in Thai HIV-1 experienced cases that have been treated with at least one of each available ARV classes.*
Results: *Twenty-three patients were recruited from five participating centers. Seventeen patients (74%) completed 96 weeks of the treatment. Six patients prematurely withdrew from the present study in which three expired from HIV related complications, two withdrew consents, and one from adverse event. The most common adverse event is injection site reactions, which occurred in 22 patients. The manifestations and intensity varied from rash, erythema, edema, pain, induration, and bleeding at the injection sites, to inflammatory nodules. Most of the patients tolerated the treatment well. Enfuvirtide administered along with other antiretroviral combination provided a good control of the disease.*
Conclusion: *Enfuvirtide was well tolerated by Thai patients who participated in the present study. The adverse events did not compromise the patient compliance.*

Keywords: *Enfuvertide, Injection site reaction, HIV drugs resistance, Compassionate use program*

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Upscale use of antiretroviral therapy (ART) in resource-limited countries has dramatically decreased morbidity and mortality of HIV-1 related opportunistic infections[1]. However, there are many problems related to the caring of HIV infected people who have received ART, *e.g.* well-known side effects to various body systems due to the use of relatively toxic ART, and the lack of immunologic and virologic monitoring have resulted in delay of HIV resistance detection. With limited available options of ART or constraint of financial reimbursement for many health care programs, these patients are continuing to suffer from the disease. In 2004, Thailand had only three classes of ART available, Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs). Non-adherence and under monitoring of $CD4^+$ cell counts and plasma HIV RNA viral load had led many patients to develop virological failure and lost the opportunity to recycle their ART due to HIV mutation codons accumulations[2,3]. Enfuvertide compassionate use program supported by Roche Thailand, Ltd was initiated in 2004 in order to salvage HIV-1 infected patients who had been exposed and developed HIV drug resistance to at least one of each ARV classes. The drug was given along with available other ART chosen by invertigators.

Correspondence to:
Prasithsirikul W, Department of Medicine, Bamrasnaradura Infectious Disease Institute, Ministry of Public Health, Nonthaburi 11000, Thailand
Phone: 0-2590-3408, Fax: 0-2590-3411
E-mail: drwisit_p@yahoo.com

Enfuvertide (FUZEON, T-20), a fusion inhibitor, was been approved by the US FDA in March 2003 for treatment of HIV infected people who have ongoing viral replications in spite of highly active antiretroviral therapy. Primary sequence of Enfuvertide was derived from a naturally occurring motif (amino acid residues 643-648) within the gp 41 transmembrane glycoprotein of HIV-1. *In vitro*, Enfuvertide exhibits potent and selective inhibition of de novo regulation of the fusion of HIV-1 to host cell membranes[4-6]. Enfuvertide is the first drug that specifically inhibits the function of the gp 41 transmembrane glycoprotein of HIV-1. Two randomized studies, TORO 1 and TORO 2 (T-20 vs. Optimized Regimen Only), proved the efficacy of Enfuvertide in providing a significant and additional decrease in the amount of virus in the blood compared to an individualized antiretroviral treatment regimen alone[7-9]. Since Enfuvertide is administered by an injection route, unlike the other classes of antiretrovirals that are given orally. Reactions are frequently observed at the injection site. The authors would like to assess Enfuvertide safety and tolerability when it was used in the salvage therapy of Thai HIV-1 resistant cases during the two years of the compassionate program.

Material and Method

An open-label, non-comparative study was conducted between 2004 and 2006 in 23 HIV-infected patients who had resistance to all of the three classes of antiretrovirals, at least one drug of each class, available in Thailand. The patients were enrolled from five centers (Bamrasnaradura Infectious Disease Institute, Bumrungrad International Hospital, King Chulalongkorn Memorial Hospital, Maharaj Nakorn Chiang Mai Hospital and Siriraj Hospital). All subjects signed informed consent forms. The present study received approval from The Ethical Review Committee for Research in Human Subjects. Ministry of Public Health, Thailand (Ref No.2/2547). Enfuvertide was administered with free choices of antiretroviral regimens as judged by the investigators based on the resistant profile of each individual and the reimbursement status. Video demonstrating how to administer Enfuvertide and how to adjust the lifestyle was provided to assist the investigators and study-nurses to educate each patient. Enfuvertide was dosed at 90 mg subcutaneously twice daily. All of them were informed about the injection site reactions and other potential adverse events. Schedule for clinic visits were at weeks 2, 4, 8, 12 and then every 12 weeks until the end of treatment at week 96. At each clinic visit, the patients received a physical examination, routine chemistry, hematology testing and assessment of adverse events. Frequency and timing of $CD4^+$ cell counts and HIV RNA viral load testing were done according to each center's clinic practice. Extra visits due to any adverse events were also recorded.

Results

Twenty-three patients were enrolled in the present study between February 2004 and December 2006. Seventeen patients completed the 96 weeks of treatment. Six patients withdrew prematurely. Nineteen patients were male and four were female with the mean age of 42.2 years old (SD = 8.6). Regarding HIV RNA levels, nine patients had less than 75,000 copies/ml, 10 patients between 75,000-100,000 copies/ml and four patients more than 100,000 copies/ml. The majority of the patients (17 out of 23 cases) had the level of $CD4^+$ cells counts less than 50 cells/mm^3. Baseline patient characteristics are listed in Table 1.

All patients had resistant HIV strains and had been treated with various agents within the class of NRTIs, NNRTIs and PIs. Twenty-three patients have been treated with NRTIs and PIs, whereas twenty-one patients with all three classes of agents including NNRTIs. The patients experienced NRTIs, NNRTIs and PIs ranging from 3 to 7, 1 to 2 and 1 to 6 agents, respectively (Fig. 1). Stavudine was the most frequently used NRTI whereas Indinavir was the most frequently used PI. Both Efavirenz and Nevirapine were equally used NNRTIs in the present cohort. The list of ART co-administered with Enfuvertide is shown in Table 2.

AIDS defining events

There were 33 episodes of AIDS defining events occurring in 23 cases in the present study.

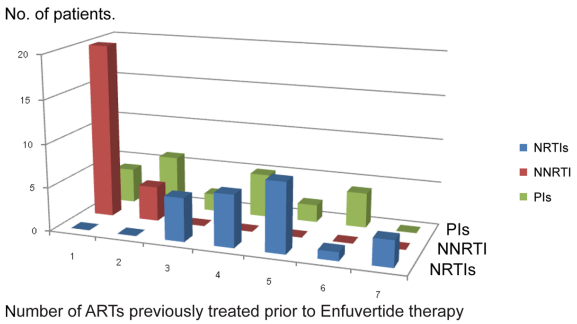

Fig. 1 The number of ARTs used prior to Enfuvertide therapy

The most common opportunistic infection was tuberculosis (13 episodes), followed by cryptococcal infections, *Pneumocystis Jirovicii* pneumonia, cytomegalovirus retinitis, and Mycobacterium avium complex infections (5, 5, 3 and 3 episodes, respectively). There was no neoplastic disease reported in the present study.

Adverse events

One hundred twenty six adverse events were reported from 23 cases. Injection site reactions were the most common and the tolerable adverse events occurred in 22 patients (95.7%). The events and severity varied from induration, pain, swelling, rash, and bleeding at injection sites, to the development of nodules and/or inflammatory nodules (Table 3). Most of the patients tolerated the injection site reactions well except one patient who withdrew from the present study due to this side effect. Other common adverse events were diarrhea and upper respiratory tract infections. There were 11 serious adverse events reported from six patients. These events were related to HIV disease and its complications such as severe anemia, cellulitis, skin infections, acute pancreatitis, acute diarrhea, acute severe abdominal pain, acute colitis, immune reconstitution inflammatory syndrome, bronchiectasis, brain mass, and brainstem stroke. Seventeen patients completed 96 weeks treatment and six patients prematurely withdrew from the present study. Among the withdrawal cases, three of them expired, two withdrew consent due to personal reason, and one withdrew from adverse event.

Immunologic and virologic responses to the treatment

The design of the present study was to assess the safety and tolerability of Enfuvertide in Thai HIV patients who were heavily treated with many classes of antiretroviral agents. It was not designed to assess the immunologic and virologic status of the patients. For this reason, $CD4^+$ cell counts and HIV RNA levels of these patients were not uniformly monitored. However, a subgroup of the patients who had followed-up on $CD4^+$ cell counts and HIV RNA level were recorded (n = 19). Eight out of 19 cases and five out of 17 cases achieved viral suppression of HIV RNA level less than 50 copies/ml at week 48 and week 96, respectively. At the end of the treatment, the increase of $CD4^+$ cell counts from baseline ranged from 30-422 cells/mm3was observed in five cases who had baseline HIV RNA level less than 50 copies/ml (Table 4).

Table 1. Baseline characteristics of 23 HIV-infected patients

Baseline characteristics	
Demographics	
Age, mean ± SD, year	42.2 ± 8.6
Male gender, number (%)	19 (82.6)
Laboratory parameters	
Plasma HIV RNA, copies/ml, number (%)	
< 75,000	9 (39)
75,000-100,000	10 (43.5)
> 100,000	4 (17.5)
$CD4^+$ cell counts, cell/mm^3, number (%)	
< 50	17 (73.9)
50-100	2 (8.7)
> 100	4 (17.3)

Table 2. List of ARTs co-administered with Enfuvertide

No. of patients with NRTIs (n = 23)		No. of patients with PIs (n = 23)		No. of patients with NNRTIs (n = 23)	
ARTs	Frequency	ARTs	Frequency	ARTs	Frequency
Stavudine	21	Indinavir	2	Efavirenz	13
Didanosine	20	Indinavir/ritonavir	15	Nevirapine	12
Zidovudine	19	Ritonavir	15		
Lamivudine	17	Saquinavir soft gel	14		
*Zidovudine + Lamivudine	11	Lopinavir/ritonavir	14		
Abacavir	11	Nelfinavir	7		
Zalcitabine	7	Saquinavir hard gel	5		
*Stavudine + Lamivudine + Nevirapine	2	Amprenavir	2		

* Fixed-dose combination

Table 3. Types of injection site reaction related to Enfuvertide injection and percentage of events due to injection site reaction from the total number of adverse events

Types of injection site reaction	Number of events (%)
Pain	14 (11)
Induration	14 (11)
Inflammatory nodules	9 (7)
Bleeding	6 (4.8)
Rash	5 (4)
Local swelling	4 (3.2)
Erythrema	3 (2.4)
Ecchymosis	2 (1.6)
Total number of events due to injection site reaction	57 (45.2)
Total number of adverse events	126

Table 4. Immunologic response to Enfuvirtide in 5 patients who had HIV RNA level < 50 copies/ml at the end of the study (96 weeks)

Patients	$CD4^+$ cell counts ($cell/ml^3$)		Increase of $CD4^+$ cell counts from baseline ($cell/ml^3$)
	Week 0	Week 96	
1	5	427	422
2	39	112	73
3	16	173	157
4	134	164	30
5	135	187	52

Discussion

The present Enfuvertide study was initiated to assist Thai patients who had resistant HIV while on current antiretroviral therapies with the aims to control HIV replication, improve immunological status, and delay clinical progression. The present study had helped the patients to stay under control for a few years before the new generations of NNRTIs, PIs, new ARV classes and any HIV specific reimbursement program from the government would be available. Due to the design of the present study, it is difficult to control or standardize the backbone ART of these patients and the investigators were allowed to choose any appropriate ART for their patients and add Enfuvertide to the regimens in order to control or improve the outcome of HIV disease. The primary objective of the present study was to assess the safety and tolerability of Enfuvertide when used in the real life situation in a resource-limited country. Another concern for the investigators prior to screening the patients was to inform the patients of route of administration of Enfuvertide. Subcutaneous injection twice daily is not an easy route and requires patient's co-operation. A video demonstrating how to administer Enfuvertide and how to adapt lifestyle was very useful in assisting the investigators and study nurses when educating the patients.

Between February 2004 and December 2006, 23 patients were recruited in the present study from five study centers. Seventeen patients completed the 96 weeks of treatment while six patients were prematurely withdrawn. Injection site reactions were the most common adverse events observed. The manifestations and severity at the injection sites varied from induration, pain, swelling, to developing inflammatory nodules (Fig. 2). However, the patients had generally tolerated the adverse events well and complied with the treatment except for one patient who withdrew due to the injection site reactions. The recent review article by Marr P et al[10] summarized the use of Enfuvertide with all other ARTs. Adding

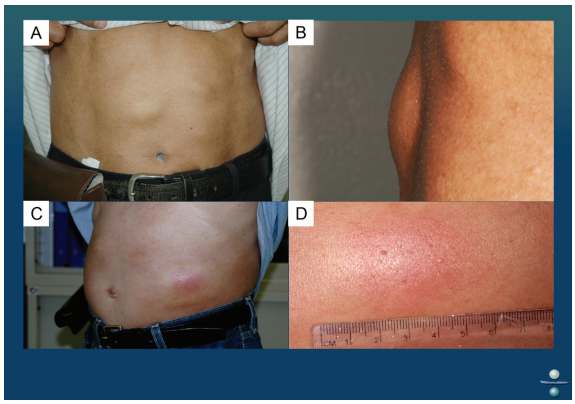

Fig. 2 An example of local site reaction of Enfuvirtide injection
Injection site reaction of Enfuvertide: A and B show the front view and the lateral view of nodules which was caused by Enfuvertide injection of the same patient after two-hour injection. C and D show the front view and the closed up lesion of inflammatory nodule at the injection site after four hour injection in the same patient. The patient could tolerate this adverse event and maintain. Enfuvertide injection until the end of the study because this injection site reaction gradually subsides over the time

Enfuvertide to the oral ART improves the disease control and maintains the viral suppression.

Conclusion

The treatment of Thai resistant HIV-1 infected patients with relatively low $CD4^+$ cell counts with Enfuvertide in addition to any appropriate ART is well tolerated. The adverse event did not compromise the patient compliance.

Acknowledgements

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Potential conflicts of interest

None.

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การศึกษา 2 ปี ด้านความปลอดภัยและการทนต่อยาเอนฟูเวอร์ไทด์ในผู้ป่วยเอชไอวีชาวไทยที่มีภาวะดื้อยาต้านไวรัส

วิศิษฏ์ ประสิทธิศิริกุล, มัทนา หาญวนิชย์, สุรพล สุวรรณกูล, วินัย รัตนสุวรณ, ถนอมศักดิ์ เอนกธนานนท์, วิชัย เตชะสาธิต, ขวัญชัย ศุภรัตน์ภิญโญ, อัสดา วิภากุล

วัตถุประสงค์: *เพื่อประเมินความปลอดภัยและทนต่อยาเอนฟูเวอร์ไทด์ในผู้ป่วยเอชไอวีชาวไทย ที่มีภาวะดื้อยาต้านไวรัส*

วัสดุและวิธีการ: *การศึกษาแบบเปิดฉลาก ไม่มีกลุ่มเปรียบเทียบโดยการให้ยาเอนฟูเวอร์ไทด์ร่วมกับยาต้านไวรัสพื้นฐานตามความเหมาะสม ซึ่งแพทย์ผู้ดูแลเป็นผู้ตัดสินใจสั่งจ่ายสูตรยา ต้านไวรัสและทำการติดตามผลข้างเคียงที่เกิดขึ้น เพื่อประเมินความปลอดภัยและความทนต่อยาเป็นเวลา 96 สัปดาห์*

ผลการศึกษา: *จำนวนผู้ป่วยที่เข้าร่วมโครงการวิจัยทั้งหมด 23 ราย โดยเป็นผู้ป่วยซึ่งติดเชื้อเอชไอวีที่มีภาวะดื้อยาต้านไวรัสจากโรงพยาบาลที่เข้าร่วมการศึกษาจำนวน 5 แห่ง ได้รับยาเอนฟูเวอร์ไทด์ ร่วมกับยาต้านไวรัสพื้นฐาน ซึ่งแพทย์ผู้รักษาเป็นผู้พิจารณาเป็นเวลา 96 สัปดาห์ โดยผู้นิพนธ์ทำการติดตามผลข้างเคียง และการทนต่อยาของผู้ป่วยเหล่านี้ พบว่ามีผู้ป่วย 17 ราย ที่สามารถรับยาเอนฟูเวอร์ไทด์จนครบ 96 สัปดาห์ และผู้ป่วย 6 ราย ออกจากการศึกษาก่อนครบกำหนด เนื่องจากเสียชีวิตจากภาวะแทรกซ้อนของการติดเชื้อเอชไอวี, เหตุผลส่วนบุคคล และทนต่อภาวะข้างเคียงของยาเอนฟูเวอร์ไทด์ไม่ได้ จำนวน 3, 2 และ 1 ราย ตามลำดับ*

ผลข้างเคียงที่พบบ่อยที่สุด คือ การเกิด injection site reaction ซึ่งเกิดขึ้นในผู้ป่วย 22 ราย มีการเกิดได้หลากหลายรูปแบบและมีความรุนแรงแตกต่างกัน ได้แก่ pain, induration, local inflammatory nodules, bleeding, rash, local swelling, erythema, ecchymosis โดยผู้ป่วยส่วนใหญ่สามารถทนต่อผลข้างเคียงดังกล่าวได้ดี เนื่องจากภาวะดังกล่าวจะลดระดับความรุนแรงลง เมื่อฉีดยาเอนฟูเวอร์ไทด์เป็นเวลานานขึ้น

การให้ยาเอนฟูเวอร์ไทด์ร่วมกับยาต้านไวรัสพื้นฐานตามแพทย์สั่งจ่าย มีแนวโน้มควบคุมระดับ HIV RNA ในผู้ป่วยได้ และช่วยให้ความรุนแรงของการติดเชื้อเอชไอวีลดลง

สรุป: *ผู้ป่วยเอชไอวีที่มีระดับเม็ดเลือดซีดี 4 ค่อนข้างต่ำและมีภาวะดื้อยาต้านไวรัส สามารถทนต่อผลข้างเคียงของยาเอนฟูเวอร์ไทด์ได้ดี เป็นเวลา 96 สัปดาห์ แม้ว่าจะพบผลข้างเคียงจากการเกิด injection site reaction ได้บ่อย*