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Switch from Enfuvirtide to Raltegravir in Virologically Suppressed HIV-1 Infected Patients: Effects on Level of Residual Viremia and Quality of Life

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Abstract

Background—Raltegravir is a potential treatment option for virologically suppressed HIV-1 infected patients on enfuvirtide with injection site reactions.

Objectives—To characterize safety and efficacy of an enfuvirtide to raltegravir switch including changes in T cells, quality of life, and residual viremia.

Study Design—In patients with viral load <50 copies/mL and injection site reactions, enfuvirtide was switched to raltegravir without additional changes to the antiretroviral regimen. Virologic failure was defined as a viral load >1000 copies/mL or two consecutive viral load measurements between 50–1000 copies/mL (low-level viremia). Over the 24 week study, we compared changes in T cells, injection site reactions, quality of life, and residual viremia, as measured through the single-copy assay which can detect plasma virus down to a single copy, using paired t-tests.

Results—Fourteen patients with a median CD4+ T-cell count of 420 cells/μL were enrolled. After the switch, two patients experienced virologic failure due to confirmed low-level viremia. However, both patients subsequently were resuppressed, one without any changes to his regimen. There was no change in CD4+ T-cell count. Injection site reactions resolved. However, there was little reported change in quality of life. The baseline median level of residual viremia was 6 copies/mL and did not change after the switch to raltegravir.

Conclusions—A switch to raltegravir in virologically suppressed patients on enfuvirtide is effective in maintaining immunologic and virologic control at 24 weeks but did not result in a change in residual viremia.

Keywords

HIV infections/*virology; enfuvirtide; raltegravir; patient satisfaction; skin/drug effects

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Background

In 2003, enfuvirtide was approved for use in HIV-1 infected treatment-experienced individuals, but its use is complicated by injection site reactions.^{1, 2} Over time, injection site reactions can become increasingly painful and lead to scarring and atrophy of subcutaneous tissues, making it difficult to find a location to effectively deliver the medication. The needle-free Biojector delivers enfuvirtide subcutaneously with compressed carbon dioxide and can reduce but does not eliminate injection site reactions.³

The integrase inhibitor raltegravir has demonstrated efficacy in treatment-naïve and treatment-experienced patients with few associated adverse effects.^{4, 5} As such, raltegravir may represent an excellent alternative for patients with injection site reactions on enfuvirtide. Retrospective studies have reported favorable outcomes in virologically suppressed patients switched from enfuvirtide to raltegravir^{6, 7}, but to-date no prospective studies have been published. In patients on older antiretroviral regimens, over 80% with a viral load < 50 copies/mL as measured by the standard ultra-sensitive assay have detectable virus on the single-copy assay, a highly sensitive assay which quantifies persistent viremia in plasma down to a single copy.⁸ However, relatively little is known regarding the level of residual viremia in patients on newer antiretroviral agents such as enfuvirtide and raltegravir.

Objectives

The present study evaluates the changes in viral load, T cells, injection site reactions, quality of life, and residual viremia associated with a switch from enfuvirtide to raltegravir in virologically suppressed HIV-1 infected patients.

Study Design

We enrolled virologically suppressed HIV-1 infected patients with injection site reactions for a switch from enfuvirtide to raltegravir. At baseline, enfuvirtide was switched to raltegravir without additional changes to the antiretroviral regimen allowed. Viral load, T cells, and toxicity labs were evaluated at baseline, 2, 4, 12, and 24 weeks.

Adherence and injection site reactions were evaluated at baseline, 4, 12, and 24 weeks using the self-administered AIDS Clinical Trials Group adherence survey⁹ and an injection site reaction rating scale developed for the TORO studies, respectively.^{1, 2} Quality of life was measured at entry and 24 weeks using the MOS-HIV Health Survey which has 11 domains (General Health Perceptions, Physical Functioning, Role Functioning, Social Functioning, Cognitive Functioning, Pain, Mental Health, Energy, Health Distress, Quality of Life, and Health Transition), each on a hundred point scale.¹⁰

The single-copy assay was used to measure HIV RNA levels at screening, baseline, and at 12 and 24 weeks. The methods for the assay have been described elsewhere.¹¹ The mean of the screening and baseline level of residual viremia on the single-copy assay were used for the pre-switch value and the mean of the 12 and 24 week values were used for the post-switch value.

For entry, patients were required to be on an enfuvirtide-containing antiretroviral regimen with a viral load <50 copies/mL for at least 6 months, excluding blips (e.g., single viral load measurement of 50-1000 copies/mL). Other inclusion criteria included CD4+ T-cell count $\geq 50/\mu\text{L}$, absolute neutrophil count $\geq 750/\mu\text{L}$, hemoglobin $\geq 10 \text{ g/dL}$, platelets $\geq 50,000/\mu\text{L}$, calculated creatinine clearance $\geq 30 \text{ mL/min}$, and AST, ALT, and alkaline phosphatase $\leq 5 \times$ upper limits of normal.

Exclusion criteria included an unstable clinical condition such as cancer requiring therapy, an opportunistic infection within 60 days prior to entry, receipt of any vaccination within 30 days prior to study entry, or plan for receipt of any vaccination during the study.

The primary outcome was virologic failure which we defined as confirmed low-level viremia (e.g., two consecutive viral load measurements between 50-1000 copies/mL) or a single measurement of viral load >1000 copies/mL. In patients with low-level viremia, a confirmatory viral load was obtained as soon as possible after the first determination, preferably within 2 weeks after the first sample. Secondary outcomes included change in CD4+ T-cell count, CD4+ T-cell percent, injection site reactions, quality of life, residual viremia on the single-copy assay, and occurrence of clinical or laboratory adverse events.

We used paired t-tests to evaluate changes associated with the switch using Stata 9 (College Station, Texas). Significance was assessed at the $p < 0.05$ level. Patients provided written informed consent prior to entry. Stanford University's Institutional Review Board approved the protocol.

Results

Fourteen patients, all men, were enrolled (Table 1). The median age was 56 years with 50% having prior AIDS diagnoses. Patients had received a median of 6 NRTIs, 1 NNRTI, 4 PIs, and enfuvirtide for 26 months prior to study entry. Based on the IAS-USA mutation list,¹² the patients' most recent genotypic resistance test had a median of 7 NRTI, 1 NNRTI, and 4 major PI mutations. Besides enfuvirtide, their antiretroviral regimen contained a median of 2 NRTIs, a NNRTI in 5 patients, and a ritonavir-boosted PI in 12 patients. Excluding blips, patients had maintained a viral load <50 copies/mL for a median of 20 months prior to the switch. The median CD4+ T-cell count and CD4+ T-cell percent was 420 cells/ μL (IQR 328, 541) and 21% (IQR 18, 24), respectively. Patients had a median of 9 injection site reactions. The median level of residual viremia at baseline was 6 copies/mL (IQR 1-9).

Following the switch from enfuvirtide to raltegravir, two of 14 (14%) patients met the study definition for virologic failure, both based on confirmed low-level viremia (Table 2). One patient had a viral load of 76 copies/mL and 56 copies/mL at week 4 and week 7, respectively, and subsequently re-suppressed without any changes to his therapy. The other patient had a viral load of 380 copies/mL and 140 copies/mL at week 24 and week 26, respectively. After changing his regimen from lopinavir/ritonavir, raltegravir, and abacavir/lamivudine to darunavir/ritonavir, raltegravir, and tenofovir/emtricitabine, the patient re-suppressed to viral load <50 copies/mL. Both patients reported 100% adherence to antiretrovirals prior to experiencing viremia.

CD4+ T-cell profile over the course of the study was stable. The median change in CD4+ T-cell count was -14 cells/ μ L (IQR -90, 60; $p=0.56$). Median CD4+ T-cell percent change was -1 (IQR -2, 0; $p=0.34$). Injection site reactions from enfuvirtide generally completely resolved during the study. Twelve patients had complete resolution of all injection site reactions, mostly by 4 weeks.

Despite the improvement in injection site reactions and patients reporting improved satisfaction with their new treatment regimen, quality of life improved only minimally during the study. Evaluating changes from baseline, 7 of the 11 domains showed numeric improvement, 3 showed slight declines, and 1 domain was unchanged. However, only "Health Transition" which compares one's physical and emotional condition to a month prior showed a significant improvement compared to baseline (+23; 95% CI +3, +42; $p=0.03$).

The median change in the level of residual viremia was 0 copies/mL (IQR -6, +2; $p=0.56$). Higher levels of residual viremia at baseline did not predict patients who subsequently had detectable viral load (e.g., blips or virologic failure; data not shown).

The switch from enfuvirtide to raltegravir was well tolerated with no Grade 3 or 4 clinical or laboratory adverse events during the study. Adherence during the study was excellent with all patients reporting 95% adherence to their HIV medications.

Discussion

In this small prospective study, using stringent criteria, 2 of 14 patients developed virologic failure after the switch from enfuvirtide to raltegravir. In other switch studies using similar criteria, rates of virologic failure range from 5-20%.¹³⁻¹⁵ The definition of virologic failure in clinical studies vary.^{5, 16-18} Current guidelines emphasize maximal virologic suppression for all patients, as persistent low-level viremia can lead to high-grade virologic failure.¹⁹ Combining the two retrospective switch studies of enfuvirtide to raltegravir, 2 of 50 patients developed low-level viremia on raltegravir.^{6, 7} A recent abstract reported similar rates of continued virologic suppression in patients randomized to continue enfuvirtide or those switched to raltegravir.²⁰

The randomized studies SWITCHMRK 1+2 reported increased virologic failure in virologically-suppressed patients switched to raltegravir compared to continued lopinavir/ritonavir.²¹ The increased rates of virologic failure seen in the SWITCHMRK studies are likely due to inadequate background antiretroviral support for raltegravir, a medication with a relatively low genetic barrier to resistance when compared to boosted protease inhibitors. On the other hand, enfuvirtide and raltegravir have similar genetic barriers to resistance, and patients in our study likely had adequate background therapy to support raltegravir. An evaluation of the relative potency of various antiretrovirals using the instantaneous inhibitory potential showed enfuvirtide and raltegravir have similar potencies, while protease inhibitors are relatively more potent at clinically relevant concentrations.²²

Patients maintained stable CD4+ T-cell counts after the switch from the entry inhibitor enfuvirtide to raltegravir. The other FDA-approved entry inhibitor, maraviroc, has been

shown to have superior immunologic responses to comparator drugs after controlling for viral load response.²³ In this study after discontinuation of enfuvirtide, there was no significant decline in the CD4+ T-cell count with raltegravir.

Only 1 of the 11 quality of life domains significantly improved during the study. Discontinuation of enfuvirtide and resolution of injection site reactions did result in patients reporting improved treatment satisfaction but did not translate into measurable improvements in quality of life. The MOS-HIV survey was developed and validated in the pre-HAART era in symptomatic patients¹⁰ and may lack validity in patients well-controlled on antiretrovirals. Other switch studies to more convenient or tolerable regimens also have shown little improvement in QOL but have reported improved treatment satisfaction.^{13,24}

Similar to others, we found the majority of patients with viral load <50 copies/mL have quantifiable residual viremia.^{8, 25} In early studies, the persistence of unintegrated 2-long terminal repeat circles of HIV-1 DNA, unspliced viral mRNA, and significant viremia in sanctuary sites suggested persistent low-grade viral replication as one source of this residual viremia.^{26, 27} Others have found the level of residual viremia to be regimen-independent with no viral evolution, supporting release of non-replicating virus from latent reservoirs as a source for this residual viremia.^{8, 28} However, prior studies evaluating residual viremia were performed in patients on older regimens (generally PI-based) that target different steps in the viral life cycle. We did not see any significant decline in the level of residual viremia after the switch to raltegravir. The stability despite the change to a new antiretroviral agents argues against cryptic replication and provides further supports that release of virus from a long-lived cell type is the source for this residual viremia.

The rapid early declines in viral load seen with integrase inhibitors-containing regimens do not appear to translate into further declines in viral loads in chronically suppressed patients.^{29, 30} A small intensification study recently reported no change in the level of residual viremia with the addition of raltegravir in patients with viral load <50 copies/mL.³¹ Two larger ongoing randomized controlled trials are evaluating the effect of raltegravir intensification on the level of residual viremia in patients with a viral load <50 copies/mL,³² but based on our results, we are skeptical that additional suppression will be demonstrated.

In summary, this prospective study of an enfuvirtide to raltegravir switch in virologically suppressed HIV-1 infected patients proved safe and effective. Virologic control was maintained with stable immune status. There appeared to be no change in the level of residual viremia as measured by the single-copy assay after the switch. Raltegravir offers an excellent option for patients with virologic suppression on enfuvirtide who are experiencing injection site reactions.

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Table 1
Demographic and Baseline Characteristics of Study Patients (n=14)^I

Gender	
Male	14/14 (100%)
Female	0/14 (0%)
Median Age (IQR)	56 (45, 61)
Ethnicity	
Caucasian	12/14 (86%)
Hispanic	2/14 (14%)
AIDS diagnosis	7/14 (50%)
Prior Antiretroviral History	
Median #NRTIs (IQR)	6 (6, 7)
Median #NNRTIs (IQR)	1 (1, 2)
Median #PIs (IQR)	4 (3, 5)
Median Months on Enfuvirtide (IQR)	26 (17, 44)
Median # of Mutations on Most Recent Genotype	
NRTI mutations (IQR)	7 (5, 8)
NNRTI mutations (IQR)	1 (0, 2)
Major PI mutations (IQR)	4 (3, 6)
Background Therapy	
Median #NRTIs in Regimen (IQR)	2 (2, 2)
Receiving NNRTIs	5/14
Efavirenz	5/14
Receiving PI/r	12/14
DRV/r	7/14
LPV/r	4/14
ATV/r	1/14
Median Length of Suppressed Viral Load (IQR)	20 (15, 31)
Median CD4+ T-cell count (cells/ μ L; IQR)	420 (328, 541)
Median CD4+ T-cell Percent (IQR)	21 (18, 24)
Median Number of Ongoing ISRs (IQR)	9 (6, 12)
Residual Viremia (IQR)	6 copies/mL (1-9)

^I PI/r=ritonavir-boosted PI; DRV=darunavir; LPV=lopinavir; ATV=atazanavir; ISR=injection site reaction

Week 24 Results²**Table 2**

Virologic Failure	2/14 (14%)
Median Change in CD4+ T-cell count (IQR)	-14 cell/ μ L (-90, 60; p=0.56)
Median Change in CD4+ T-cell Percent (IQR)	-1 (-2, 0; p=0.34)
Median Time to Resolution of ISRs (IQR)	4 weeks (4, 24)
Change in Mean Quality of Life (Scale to 100)	
General Health Perceptions (95% CI)	-2 (-8, +5; p=0.56)
Physical Functioning (95% CI)	+10 (-32, +51; p=0.63)
Role Functioning (95% CI)	-7 (-23, +8; p=0.34)
Social Functioning (95% CI)	+6 (-5, +16; p=0.26)
Cognitive Functioning (95% CI)	+2 (-3, +8; p=0.43)
Pain (95% CI)	-2 (-8, +5; p=0.61)
Mental Health (95% CI)	0 (-4, +4; p=0.89)
Energy/Fatigue (95% CI)	+7 (-2, +15; p=0.10)
Health Distress (95% CI)	+1 (-6, +7; p=0.82)
Quality of Life (95% CI)	+3 (-17, 22; p=0.78)
Health Transition (95% CI)	+23 (+3, +42; p=0.03 [*])
Median Change in Residual Viremia (IQR)	0 copies/mL (-6, +2; p=0.56)

*
p<0.05;

²ISR=injection site reactions