Beneficial Effects of a Switch to a Lopinavir/rit (LPV/r)-Containing Regimen for Patients With Partial or No Immune Reconstitution With HAART Despite Complete Viral Suppression

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Introduction

Objectives

The purpose of this study was to determine if changing to a LPV/r–containing regimen resulted in greater immune reconstitution in patients with sub-optimal immune responses to HAART despite complete viral suppression.

Methods

Ten patients with partial or no immune response with HAART despite durable viral suppression, mean CD4+ count 211/mm^3, were enrolled. Five were randomized to stay on their current regimen and 5 were randomized to LPV/r-containing regimen plus their current NRTI backbone. Absolute CD4+ counts, absolute naïve CD4+ counts, and percent CD38-expressing cells were measured. T cell subsets were also isolated and *ex vivo* apoptosis quantified after 72 hours in culture. Intracellular viral loads for different T cell subsets and monocytes were also determined.

Results

No patient had viral failure during the study period. Patients switched to LPV/r showed a decrease in *ex vivo* apoptosis of CD4+CD45 RA (17.1 to 8.9 % versus 19.2 to 24.9 % for arm b, p = 0.06) and CD4CD45 RO cells (20.1 to 13.2 versus 22.5 to 23.9). The mean increase in CD4+ count was 106 (from 179 to 286) for the LPV/r-containing regimen versus 35 (262 to 297) for continuation regimens. The percent naïve cells did not change. No differences in intracellular viral loads were observed before or during the study for either the LPV/r or continuation group. Baseline CD38 expression was low for patients in both arms and did not change on therapy.

Conclusions

The mean CD4+ increase for patients switched to a regimen containing LPV/r was greater compared to patients who remained on their regimen. *Ex vivo* apoptosis of both naïve and memory CD4+ cells was reduced, while no change in intracellular viral load was observed. This at least suggests that the benefit of LPV/r may be due to an immunologic effect that is independent of antiviral activity.

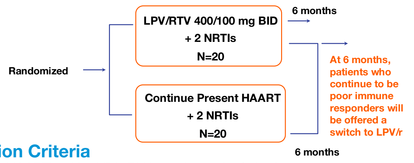
Study Background

- Immune reconstitution is a major goal of HAART
- Studies have shown that despite achieving an undetectable viral load, some patients have poor immune responses to HAART[1]
  - Immune response is an important predictor of disease progression independent of viral suppression[2]
- Our group and others have shown poor immune responses are associated with persistently accelerated T cell apoptosis[3,4]
- Evidence exists that some protease inhibitors benefit immune reconstitution independent of antiretroviral effects[5]
  - Immune reconstitution may be due in part to inhibition of T cell apoptosis[6]
- Current guidelines do not offer recommendations on changing HAART regimens when immune responses are sub-optimal
- LPV/r has demonstrated superior immune response in naïve HIV+ patients and may have utility in the treatment of experienced patients with discordant immune responses[7,8]

Study Objectives

- To determine if a change to a Lopinavir/r(LPV/r)-containing HAART regimen resulted in better immune reconstitution as measured by absolute CD4+ T cell count in patients who had only partial or no immune response to HAART despite complete viral suppression for >6 months
- To determine if the effect of LPV/r was due to an effect on T cell apoptosis
- To determine the effects of LPV/r on low level viral replication despite an undetectable plasma viral load

Study Design



Inclusion Criteria

- Stable HAART with HIV RNA <50 copies/mL for >6 months (excluding patients already on Lopinavir/r)

Definition of Immune Response:

- *Complete immune responders* post-HAART: CD4 >500 were enrolled as a control group (N=20)
- *Partial Immune Responder*: CD4 increase of ≥50 % and a ≥1 change in CD4 category*, but CD4 < 500
- *Immune non-responder*: CD4 increase <50% and < than 1 CD4 category* change (n=20)

*CD4 Categories

Group 1	<100
Group 2	100 – 199
Group 3	200 – 350
Group 4	350 – 500
Group 5	>500

Study Endpoints

Primary Endpoint

- Immune reconstitution measured as an increase in absolute CD4+ count after 1, 3 and 6 months of therapy

Secondary Endpoints

- Rates of *ex vivo* T cell apoptosis
  - CD4+ T cells (both naïve and memory)
  - CD8+ T cells
- Percent circulating PBMC subsets with detectable intracellular HIV-1 RNA
- Virologic rebound
- Clinical events

Methods

- Patients were enrolled from the outpatient clinic at University of Chicago
- Patients with partial or no immune responses were randomized to a switch to LPV/r-containing regimen or continuation of their current regimen at enrollment
- Patients were seen at entry, 1 month, 3 months, and 6 months
- Citrate- and heparin-anti-coagulated whole blood was collected for lab assays at each study visit
- T cells subsets, including % CD4, absolute CD4 count, and % CD45 were determined by flow cytometry
- Expression of CD38 (activation marker) on CD4+ T cells was also determined by flow
- Isolation and culture of specific T cell populations
  - CD4+CD45RA+ (naïve T helper cells), CD4+CD45RO+ (memory T helper cells), and CD8+ (suppressor T cells) were isolated by MACS
  - Cells were then cultured in RPMI + L-glutamine at 37° C in 5% CO_2
- *Ex vivo* apoptosis at 72 hours was determined by flow after staining with propidium iodide
- The proportion of specific peripheral blood mononuclear cell subsets were measured by the ViroTech™ HIV-1 Flow Cytometry Assay
  - PBMCs were stained with surface-directed MoAbs to determine cell type, permeabilized, and then underwent hybridization to detect intracellular HIV-1 RNA by flow cytometry
  - This testing was done as a sendout at Esoterix Laboratory Service, Inc., San Antonio, TX

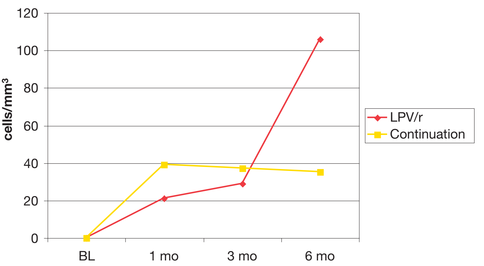
Interim Results

- To date, 10 patients with less than complete responses to HAART (6 partial immune responders and 4 immune non-responders) have been enrolled
  - 5 randomized to switch to a LPV/r-containing regimen
  - 5 randomized to continue their current HAART regimen
- Assays have been run in parallel with 38 control samples from HIV-negative healthy volunteers
- In addition, 7 complete responders (mean CD4+ 614/mm^3) have been enrolled for a one time blood draw to serve as a second control group
- The data for the partial immune responders and immune non-responders has been combined for this interim analysis

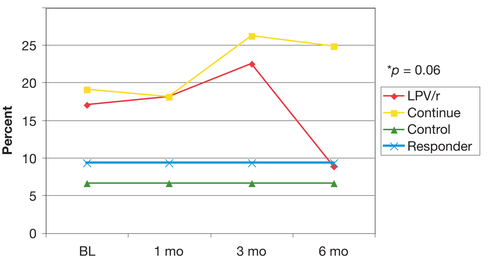
Baseline Characteristics

Variable	Switched to LPV/r-containing regimen (n=5)	Continued current HAART regimen (n=5)
Mean Age	56	33
Gender	4 males, 1 female	5 males
HAART Regimen at Enrollment		
2 NRTIs + PI	1	1
2 NRTIs + Boosted PI	0	1
2 NRTIs + NNRTI	2	2
3 NNRTIs	2	1
Mean Baseline CD4 Count (cells/mm^3)	180	228

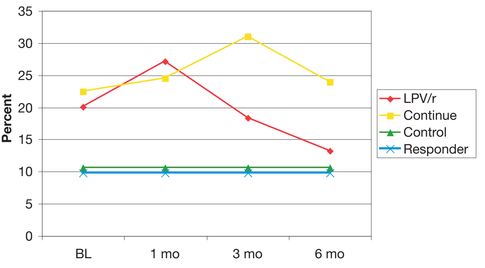
Mean Change in Absolute CD4+ Count



Percent Apoptosis CD4 CD45RA (Naïve) After 72 Hours



Percent Apoptosis CD4 CD45RO (Memory) After 72 Hours



Other Secondary Endpoints

- No trends in *ex vivo* apoptosis of CD8 T cells were observed (data not shown)
- All patients had circulating PBMCs with detectable intracellular HIV-1 RNA, but no differences in the percent positive were observed between the two treatment arms or compared to the complete responder group (data not shown)
- No subjects have had any HIV-related clinical events or grade II – IV medication-related adverse events
- All subjects maintained undetectable viral loads (HIV-1 RNA < 50 copies/mL) throughout the study

Study Conclusion

- A switch to a LPV/r-containing regimen resulted in a greater increase in CD4+ cell count over 6 months as compared to patients remaining on current regimen
- Rates of *ex vivo* T cell apoptosis were initially higher for partial immune responders and immune non-responders as compared to the complete immune responders
- LPV/r decreased *ex vivo* apoptosis of CD4 naïve and memory cells to a level similar to that of complete immune responders, and the rates for naïve cells approached statistical significance
- T cell activation as measured by CD38 expression was similar for complete immune responsders and poor immune responders at baseline, and this did not change during the study for either arm
- The beneficial immune effects of LPV/r have been independent of any anti-viral response as there were no changes in the percent of PBMCs with detectable intracellular HIV-1 RNA
- None of the subjects have had viral rebound (detectable viral load) or any clinical events during the course of the study

References

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