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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THE UNIVERSITY OF CHICAGO HOSPITALS

Abstract

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

Seventeen patients (mean CD4+=226/mm^3) with partial (9) or no immune response (8) with HAART despite durable viral suppression, mean CD4+ count were enrolled. Nine were randomized to continue their current regimen and 8 to LPV/r plus their current NRTI back-bone. Absolute CD4+ counts, absolute naïve CD4+ counts, and percent CD38+ cells were measured. T cell subsets were isolated and *ex vivo* apoptosis quantified. Intracellular viral loads for various PBMCs were also determined.

Results

Patients switched to LPV/r had a mean increase in CD4+ count of 125 (from 177 to 302) for the LPV/r-containing regimen versus 32 (264 to 289) for continuation regimens, and a mean change of 68.5% vs 14.9%, p=0.02. The percent CD4+ cells also increased. The LPV/r patients had a greater decrease in *ex vivo* apoptosis of CD4+CD45 RA (24.0 to 11.2% versus 18.5 to 20.1% for continuation, p=0.03) and CD4CD45 RO cells (23.6 to 17.8 versus 21.0 to 19.1). The percent naïve cells did not change, but the absolute number was increased. No differences intracellular in viral loads were observed before or during the study for either group. Baseline CD38 expression was low in both arms and did not change the therapy.

Conclusions

Patients switched to a regimen containing LPV/r had a greater increase in CD4+ count compared to patients who remained on their regimen. There was a significant decrease in *ex vivo* apoptosis of naïve CD4+ cells and a similar trend for memory cells. This suggests that the immune benefit of LPV/r may be due to an immunologic effect that is independent of antiviral activity.

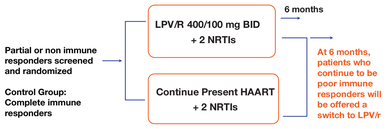
Study Background

- 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) kaletra™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 and partial or no immune response
- Not on a Lopinavir/r containing regimen

Definition of Immune Response:

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

*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 screened and enrolled in a sequential fashion from the outpatient clinic at University of Chicago
- Patients with partial or no immune responses were randomized to 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
- Citrated and heparinated whole blood was collected 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 cytometry
- 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
- In addition, we also examined ex vivo apoptosis for a group of 10 complete immune responders and 10 HIV-negative controls.
  - The complete responders were evaluated one time
  - HIV-negative controls were used as an internal standard and assays run in parallel with samples from the study cohort
- 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 performed at Esoterix Laboratory Service, Inc., San Antonio, Texas

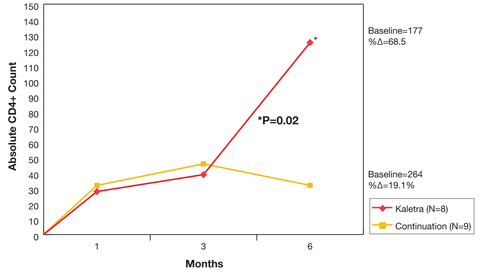
Interim Results

- 17 patents with less than complete responses to HAART. (9 partial immune responders and 8 immune non-responders) have been enrolled.
  - 8 randomized to switch to a LPV/r-containing regimen
  - 9 randomized to continue their current HAART regimen
- Assays were run in parallel with control samples from HIV-negative healthy volunteers
- In addition 10 complete responders with mean CD4 count >500 cells/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

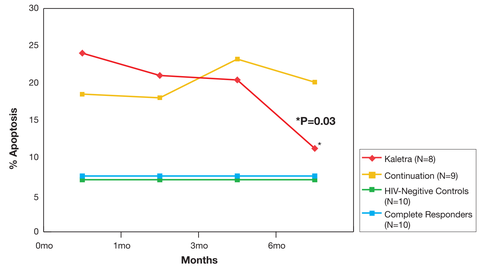
Variable	Switch to LPV/r containing regimen (n=8)	Continued current HAART regimen (n=9)
Mean Age	49.0	39.6
Gender	7 males, 1 female	8 males, 1 female
Mean CD4 Count	177	264
Immune Responders at Enrollment	4 non-responders, 4 partial responders	4 non-responders, 5 partial responders
HAART Regimen at Enrollment		
2 NRTIs + NNRTI	6	5
2 NRTIs + PI	1	1
2 NRTIs + Boosted PI	0	1
3 NRTIs	1	2

Mean Increase in CD4 Count After a Switch to Kaletra vs Continuation of HAART

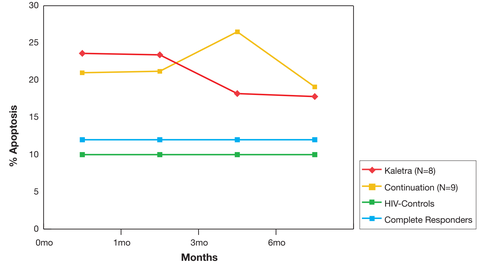


Interim Results (cont.)

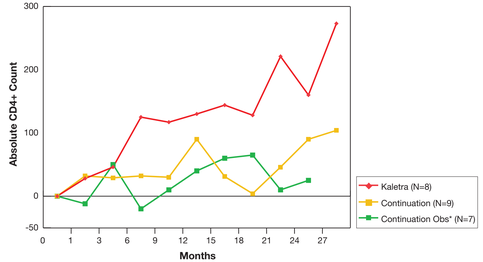
Mean Apoptosis (Percent) of CD4CD45 RA+ (Naïve) T Cells After Switch to Kaletra vs. Continuation of Current Regimen



Mean Apoptosis (Percent) of CD4CD45 RO+ (Memory) T Cells After Switch to Kaletra vs. Continuation of Current Regimen



Post Study Results: Mean Change in CD4 Count Beyond 24 Months



*CD4+ counts of 7 patients who qualified for the study, but refused to participate and continued their current regimen

Other Secondary Endpoints

- All subjects maintained undetectable viral loads (HIV-1 RNA < 50 copies/mL) throughout the study
- No subjects have had any HIV-related clinical events or grade II – IV medication-related adverse events
- 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)

Study Conclusion

- Switch to a LPV/r-containing regimen resulted in a significantly greater increase in CD4+ cell count over 6 months compared to remaining on current regimen
- Long-term follow up demonstrated continued CD4 cell increase in those switched to LPV/r vs continuation of 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 reached statistical significance
- These immune effects of LPV/r were independent of any anti-viral response as there were no changes in the percent of PBMCs with detectable intracellular HIV-1 RNA
- No subjects experienced viral rebound (detectable viral load) or significant clinical events during the course of the study

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