Poster PE9.1/4

Differences in Adverse Event Profiles in Antiretroviral-Naive Subjects Starting Antiretroviral Therapy with CD4 Counts <50 Cells/mm^3 vs. >200 Cells/mm^3: Does Immune Reconstitution Inflammatory Syndrome (IRIS) Play a Role?

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Introduction

Antiretroviral therapy may be associated with immune reconstitution inflammatory syndrome (IRIS). Patients experiencing IRIS demonstrate a paradoxical worsening of symptoms following initiation of antiretroviral therapy. This clinical deterioration correlates with virological and immunological response to therapy. The sudden reversal in immunodeficiency often results in the frequent occurrence of certain symptoms such as fever, chills, sweats, malaise, fatigue, diarrhea, nausea, and vomiting.

Symptoms of IRIS typically develop within the first 1-2 months following initiation of combination antiretroviral therapy but have been reported up to 2 years later (1). Immune reconstitution syndromes have been reported to occur in up to 25% of patients who demonstrate a response to combination antiretroviral therapy and up to 40% of responders who started therapy from a CD4+ T-cell nadir of <50 cells/mm^3 (2).

Certain adverse effects have been observed more commonly in trials of persons with more advanced HIV disease. Some of these adverse effects may be related to immune reconstitution rather than a direct toxic effect from a drug.

Lopinavir/ritonavir (LPV/r) is the preferred protease inhibitor for initiation of antiretroviral therapy in current guidelines of the U.S. Department of Health and Human Services (3). In the LPV/r development program, no restriction on baseline CD4+ T-cell count was imposed in trials of treatment-naïve subjects. We assessed whether subjects with CD4+ T-cell count <50 cells/mm^3 had a higher incidence of non-specific adverse events consistent with an acute inflammatory process (IRIS) when compared to subjects with a CD4+ T-cell count >200 cells/mm^3.

Methods

- Four studies of LPV/r-based regimens in antiretroviral-naive subjects (n=654) were included in the analysis (Studies 863, 418, 720, and 056). All patients received lamivudine or emtricitabine and 1 additional NRTI (stavudine, n=464 or tenofovir, n=190). These studies had no CD4+ T-cell count restriction, resulting in a wide range of baseline CD4+ T-cell counts.
- Subjects exhibiting evidence of acute illness and those treated with an opportunistic infection in the preceding 30 days were generally excluded from these studies.
- Adverse events during the first 4 weeks of treatment were summarized. Events were summarized at the body system level as well as the individual event level (COSTART term).
- The incidence of adverse events at the body system and individual level was compared between subjects with baseline CD4+ T-cell count <50 cells/mm^3 ("<50 group," n=123) and those with baseline CD4 T-cell count >200 cells/mm3 (">200 group," n=367). CD4+ T-cell count groups were chosen to amplify any potential difference between the groups.
- If differences between the <50 group and the >200 group were observed at Week 4, the occurrence of these events was also summarized through Weeks 8 and 12.
- A similar comparison through Week 4 was conducted in nelfinavir-treated subjects enrolled in Study 863. Subjects with CD4+ T-cell count <50 cells/mm^3 (n=55) were compared to those with CD4+ T-cell count >200 cells/mm^3 (n=184).

Results

Baseline Characteristics

- No significant differences between groups in gender, age, or race/ethnicity were observed between groups (Table 1).
- As expected, highly significant differences in baseline plasma HIV-1 RNA level and baseline CD4+ T-cell count were observed (Table 1).

Table 1. Demographics and Baseline Characteristics

	<50 Group (n=123)	>200 Group (n=367)	p-value
Male	100 (81%)	305 (83%)	0.68
Age (mean, years)	38.7	37.3	0.17
Race/ethnicity			
White	61 (50%)	218 (59%)	0.23
Black	41 (33%)	96 (26%)	
Hispanic	14 (11%)	40 (11%)	
Other	7 (6%)	13 (4%)	
Baseline Plasma HIV-1 RNA (mean, $\log_{10}$ copies/mL)	5.43	4.58	<0.0001
Baseline CD4+ T-cell count (mean, cells/mm^3)	23	419	<0.0001

Initial CD4+ T-cell Count and HIV-1 RNA Level Changes

- Mean CD4+ T-cell count increases were similar between the <50 group and the >200 group. In the <50 group, the mean increases from baseline to Weeks 4, 8, and 12 in CD4+ T-cell counts were 101, 111, and 112 cells/mm^3, respectively. Corresponding increases in the >200 group were 94, 125, and 134 cells/mm^3, respectively, with no significant differences between groups at any timepoint.
- Mean HIV-1 RNA decrease through 4 weeks was larger in the <50 group compared to the >200 group (–2.3 vs. vs. –1.7 log10 copies/mL, p<0.001), corresponding to the higher baseline levels in the <50 group.

Adverse Events by Body System

- During the first 4 weeks, similar proportions of subjects reported at least one adverse event (78% in the <50 group and 76% in the >200 group).
- Discontinuations due to adverse events during the first 12 weeks were uncommon, occurring in 2% and 4% of the <50 group and >200 group, respectively (p=0.38). Overall discontinuations during the first 12 weeks were 7% and 8%, respectively (p=0.70).
- Statistically significant differences between the <50 group and >200 group in the incidence of adverse events through 4 weeks were observed for the skin and appendages, hemic and lymphatic, and digestive systems (Figure 1).
- Differences between groups are shown over time for the skin and appendages system and the hemic and lymphatic system in Figure 2.

Figure 1. Adverse Events by Body System Through Week 4

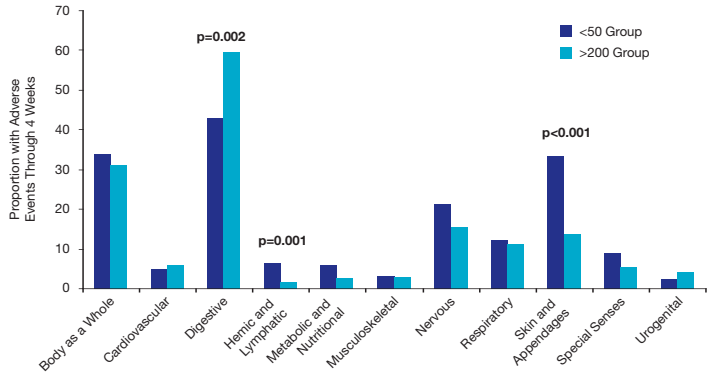
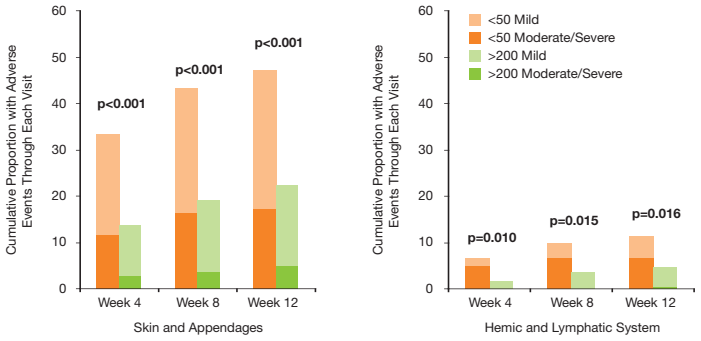


Figure 2. Adverse Events for Select Body Systems Through Week 12



Skin and Appendages Adverse Events

- In the skin and appendages body system, events of maculopapular rash, rash, seborrhea, and sweating occurred significantly more frequently in the <50 group compared to the >200 group (Figures 3 and 4).
- These individual events generally appeared to be occurring in different subjects. That is, the same subject did not generally report more than one type of skin and appendages event. For example, through 4 weeks in the in the <50 group, a total of 48 event terms were reported for 41 subjects.

Figure 3. Skin and Appendages Events

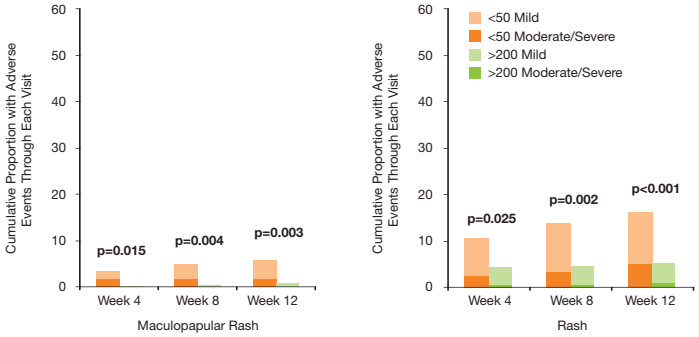
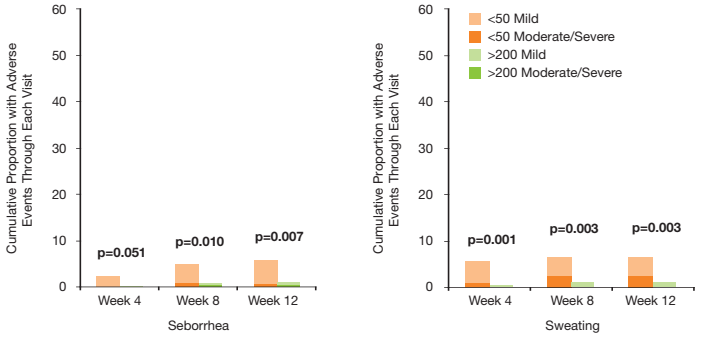


Figure 4. Skin and Appendages Events



Other Adverse Events

- Differences between groups in the hemic and lymphatic system were generally due to differences in leukopenia (Figure 5).
- Other adverse events observed more frequently in the <50 group compared to the >200 group included insomnia, conjunctivitis, and peripheral neuritis (Figures 5 and 6). Events of peripheral neuritis included events described as "peripheral neuropathy" or as pain and "itching," "tingling," or "numbness" in the extremities. All but one of these events occurred in subjects receiving stavudine.
- Differences between groups in digestive system events were generally due to higher rates of diarrhea and nausea in the >200 group (Figure 7). These events generally occurred early in the study; in both groups, there were few new-onset events after Week 4.
- Several general symptoms that might be expected during IRIS did not exhibit differences between the <50 and >200 groups, including fever, flu syndrome, headache, arthralgia, myalgia, malaise, or pain.
- Through 4 weeks of treatment, HIV-related events were more common in the <50 group, including oral candidiasis (9% vs. 1%, p<0.001), *Mycobacterium avium-intracellulare* infection (3% vs. 0%, p=0.004) and *Pneumocystis* pneumonia (2% vs. 0%, p=0.016).

Figure 5. Other Adverse Events of Interest

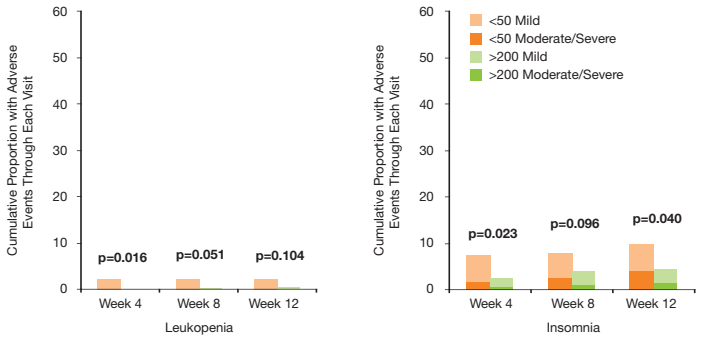


Figure 6. Other Adverse Events of Interest

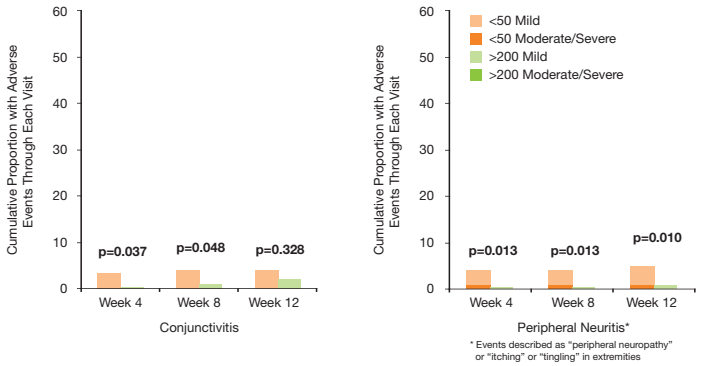
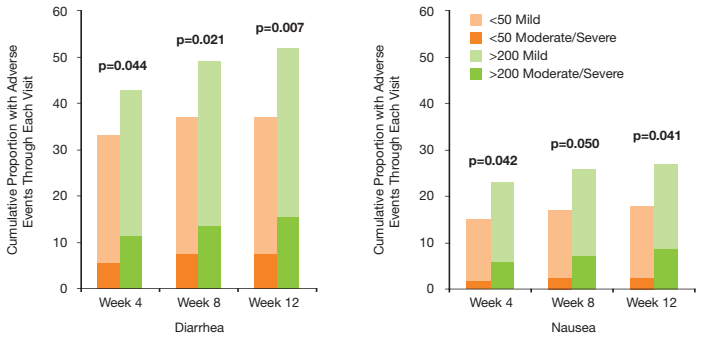


Figure 7. Digestive System Events



Adverse Events in Nelfinavir-treated Subjects

- Through 4 weeks of treatment, a similar phenomenon was observed in nelfinavir-treated subjects. Specifically nelfinavir-treated subjects with baseline CD4+ T-cell count <50 cells/mm^3 had higher rates of skin and appendages events (maculopapular rash, rash, and sweating) and insomnia, compared to subjects with baseline CD4+ T-cell counts >200 cells/mm^3. Also similar to the results in LPV/r-treated subjects, nelfinavir-treated subjects in the <50 group had lower rates of digestive system events (diarrhea in particular) compared to the >200 group.

Discussion

In the weeks immediately after treatment initiation, several symptoms including maculopapular rash, rash, sweating, conjunctivitis, insomnia, peripheral neuritis (includes stavudine-related events of peripheral neuropathy) and leukopenia occurred more commonly in subjects on LPV/r with baseline CD4+ T-cell counts <50 cells/mm^3 versus those with CD4+ T-cell counts >200 cells/mm^3. Most events were mild in intensity. Similar results were observed for a smaller cohort of nelfinavir-treated subjects. Some of these symptoms (such as rash and sweating) may be consistent with an acute inflammatory process. Peripheral neuropathy due to stavudine has been reported to occur more frequently in patients initiating stavudine with more advanced HIV disease, consistent with our findings (4).

Other adverse events including fever, flu syndrome, headache, arthralgia, myalgia, malaise or pain in general, that might be associated with an acute inflammatory process, were not seen more commonly in subjects with CD4+ T-cell count <50 cells/mm^3 vs. >200 cells/mm^3. Several reasons may explain these findings. In most studies, the first post-baseline visit was at Week 4. It is possible that events that were mild, transient, and occurred very early may not have been recalled by the subject. It may be that symptoms of IRIS are related to specific exposure to pathogens that are clinically inapparrent at the time of initiation of antiretroviral therapy. Since subjects with acute illness or recent treatment for opportunistic infections were excluded from these studies, they may not have been "exposed" or infected at the time of randomization. Finally, it may be that immune reconstitution occurs regardless of CD4+ count and that the lack of a significant difference reflects that IRIS is occurring equally in both study groups.

Somewhat unexpectedly, gastrointestinal adverse events generally and diarrhea specifically were reported more commonly in subjects with CD4+ T-cell count >200 cells/mm^3. Adverse events are defined as a worsening from the baseline condition, and since diarrhea is more common in untreated subjects with CD4+ T-cell count <50 cells/mm^3 (5), it is possible that some subjects with low CD4+ T-cell counts had diarrhea during the early period of the study that did not represent a worsening from baseline and hence did not meet the definition of an adverse event.

This analysis is limited by the fact that these studies were not specifically designed to search for symptoms associated with IRIS. Investigators and study coordinators were not given specific guidance to seek out these possible adverse events. Despite this limitation, the differences seen in possible non-specific IRIS symptoms between subjects with CD4+ T-cell counts <50 cells/mm^3 and those with CD4+ T-cell counts >200 cells/mm^3 suggests that further study in prospective clinical trials is warranted.

Conclusions

- Within the first few weeks of LPV/r-based treatment initiation, subjects with baseline CD4+ T-cell counts <50 cells/mm^3 experienced a number of symptoms at a higher frequency than subjects with CD4+ T-cell counts >200 cells/mm^3.
- Similar results were observed in nelfinavir-treated subjects.
- Several non-specific systemic symptoms that might be expected during immune reconstitution inflammatory syndrome were not observed more frequently in subjects with low baseline CD4+ T-cell counts.
- Prospective studies are needed to further characterize this phenomenon. During the first 4 weeks of therapy, more intensive questioning about non-specific symptoms may yield more consistent and definitive data.
- Proactive discussion of these potential symptoms may better prepare patients, especially those with very low CD4+ T-cell counts, for antiretroviral therapy.

References

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