

**Notification of Change to:
HPTN 052 Study-Specific Procedure (SSP) Manual, V 1.6**

Attention: HPTN 052 Investigators of Record, Study Coordinators, and site teams

Subject: Inclusion Criteria for Women on ART for pMTCT
and
Additional Information for the Use of Boosted and Unboosted Atazanavir

Date: 20 May 2009

This Notification of Change clarifies references to:

- Inclusion Criteria for Women on ART for pMTCT (Section 9.2.2.1)
- Additional Information for the Use of Boosted and Unboosted atazanavir (Section 8.2.1)

Note that a ~~strike through~~ indicates deletions and **bold** indicates additions.

Section 9.2.2.1 Screening – (page 9-2):

During the screening visit, it should be determined whether HIV-infected individuals have current or previous use of **any HIV** ART. In general, past or present use of ~~HIV~~ ART is an exclusion criterion for the study, except in the following cases:

- The use of short-course ART during pregnancy to prevent vertical transmission **is allowed at any time prior to the study, or during screening and up to the time of enrollment in the study.**

Investigators may enroll women who **are currently receiving or who have received at any time in the past** ART as part of maternal to child transmission prevention (**for any number of pregnancies**). **This includes** 7-day post-partum ART used for the prevention of NVP resistance, regardless of the precise duration or type of therapy as long as no other exclusion criteria are in place (such as concurrent therapy). No other post-partum ART exposure will be permitted. Site investigators may use their own discretion for determining the first-line therapy for any woman for whom her pMTCT ART regimen may have put her at risk for resistance (*e.g.*, single dose NVP or less than 6 months since child birth).

Section 8.2.1 Additional Information for the Use of Boosted and Unboosted Atazanavir

Concern has been raised about the use of unboosted atazanavir (ATV) because of the unavailability of ritonavir (RTV) through the HPTN 052 study. RTV-boosted ATV (ATV/r) is currently a preferred PI

component in DHHS and IAS-USA guidelines, whereas unboosted ATV is classified as an alternative PI component. In a head-to-head comparison of ATV vs. ATV/r in treatment-naive patients, rates of virologic suppression were comparable between the two arms. ATV/r was non-inferior to ATV, but the study was not powered to determine whether ATV was non-inferior to ATV/r. ATV was associated with less hyperbilirubinemia and jaundice and a more favorable lipid profile, but there were numerically more virologic failures and emergence of PI resistance in the ATV arm. This lack of PI resistance with failure of ATV/r is one of the primary reasons for current guidelines classifications. However, it should be noted that failure of ATV is typically associated only with the I50L mutation, which causes high-level resistance to ATV but not to any other PIs. In fact, I50L may be associated with PI hypersusceptibility. Thus, ATV is often felt to be the most appropriate PI to use when RTV boosting is not an option. The lower incidence of jaundice and the favorable lipid effects may help to offset the resistance issues discussed above.

Unboosted ATV should only be used in PI-naive patients, in whom trough levels of ATV will be adequate to suppress wild-type virus. Unboosted ATV can be used with zidovudine (AZT) or abacavir (ABC) but not with tenofovir (TDF), because of the reduction in ATV levels when co-administered with TDF. Although unrelated to HPTN 052, it should be noted that when ATV is combined with efavirenz (EFV), ATV requires RTV boosting at a dose of 400/100 mg once daily. ATV should not be combined with nevirapine (NVP), either boosted or unboosted.

In ACTG 5175, the combination of ATV, didanosine EC (ddI-EC) and emtricitabine (FTC) was found to be inferior to the other arms in the study, and participants in this arm were switched to other regimens. It cannot be concluded that the inferiority of this arm was due to the use of unboosted ATV. The entire regimen was problematic, as it consisted of three once-daily drugs that could not be taken together: ATV must be taken with food, whereas ddI-EC must be taken on an empty stomach. One possible explanation for the inferiority of this regimen was that patients were taking all of the components together once a day, resulting in inadequate absorption of either ATV or ddI.

In summary, unboosted ATV should be viewed as a safe and effective agent. While there are some advantages associated with RTV boosting, there are disadvantages as well. RTV boosting of ATV is not essential.

A new section, Section 8.2.1 will be added to the HPTN 052 SSP to reflect the above information.