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## FAT DISTRIBUTION AND RETINOID-LIKE SYMPTOMS ARE INFREQUENT IN NRTI-EXPERIENCED SUBJECTS TREATED WITH AMPRENAVIR.

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**BACKGROUND:** Unlike other marketed protease inhibitors (PIs), amprenavir (APV) has shown minimal effects on fat metabolism and on all-trans-retinoic acid (ATRA) signalling *in vitro*. Vitamin A derivatives such as synthetic retinoids are known to regulate lipid metabolism in fat cells and in the skin. A review of the safety database of a large phase III adult study was conducted to determine whether differences could be detected between two PIs in their propensity to cause fat redistribution or retinoid-like effects *in vivo*.

**METHODS:** PROAB3006 is a randomised study comparing the safety and efficacy of APV (1200mg BID) and indinavir (IDV, 800mg TID), in NRTI-experienced, PI-naïve adults. Combination therapy at entry was: 3TC/d4T (APV: 45%; IDV:53%), d4T/ddI (APV: 28%; IDV: 25%) and 3TC/ZDV (APV:11%; IDV: 8%). The safety database, including data from 486 (APV:245; IDV: 241) subjects treated for a median of 56 weeks (max:76 weeks), was searched for reports of fat redistribution (lipodystrophy, fat accumulation, fat wasting) and retinoid-like symptoms (*eg.* dry skin, xerostomia, taste disorders, hair or nail problems).

**RESULTS:**The following, summarises symptoms reported with a highly significant difference between treatment arms (Fisher's exact test:  $p < 0.001$ )

- *APV+NRTIs* ( $n=245$ ): Fat redistribution symptoms 8(3%), Dry Skin 7(3%), Xerostomia 3(1%), Taste Disorders 4(2%), Hair loss/alopecia 1(<1%)
- *IDV+NRTIs* ( $n=241$ ): Fat redistribution symptoms 28(12%), Dry Skin 34(14%)Xerostomia 22

(9%), Taste Disorders 20(8%), Hair loss/alopecia 16(7%)

**CONCLUSION:** These data, collected prospectively in a large randomised study in antiretroviral-experienced subjects, provide clinical evidence to support the minimal effects of amprenavir versus indinavir on ATRA signalling and fat metabolism observed in preclinical studies. A significantly lower incidence of fat redistribution and retinoid-like symptoms was reported with amprenavir than with indinavir. Also, it is possible that excess natural retinoids in the diet or synthetic retinoids given in the clinic could exacerbate the above symptoms.

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**Keywords:** AEGIS, Indinavir, Lamivudine, Sulfonamides, Stavudine, Zidovudine, HIV Protease Inhibitors, Didanosine, Reverse Transcriptase Inhibitors, Vitamin A, Tretinoin, VX 478, Adult, in vitro, supply & distribution, AIDS

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