The Effect Short Term of Con-comittant Use of Polyherbal Formulations 'Bitters' on the Bioavailability of Protease Inhibitors In Vitro and in a Wistar® Rat Model
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Purpose
HIV/AIDS being a chronic illness requires intake of medications for life, and because there is no known cure, patients generally tend to supplement orthodox medications with complimentary and traditional medicines. This study seeks to assess the bioavailability of Atazanavir/ritonavir and Lopinavir /ritonavir (PIs) in in vitro and in vivo models when concomitantly administered with marketed poly-herbal formulation Goko® bitters.

Methods
The release of Atazanavir and Lopinavir were evaluated in the presence and absence of herbal bitters studied. Goko® bitters contains Vernonia amygdalina 12% (bitter leaf) Saccharum officinarum 11.5% (sugar cane) Cajanus cajan 11.5% as the main constituents. A modified in vitro study of the release of Atazanavir and Lopinavir was evaluated using dissolution apparatus 2. In the in vivo study twenty four Wister rats were given single dose of the protease inhibitors in the presence and absence of Goko® bitters and blood samples were drawn before dosing and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 9.0, 12, 18, and 24 hours after dosing and evaluated using a HPLC. Using 10 rats per group a 14 day sub-acute toxicity test was carried out with Goko® bitters administered at 0.5mls/kg and 1.5mls/kg mimicking low and high doses together with either Atazanavir or Lopinavir. Histopathological study of the major organs, hematologic and Biochemical analysis were carried out.

Results
The presence of the bitters reduced the release of both PIs and this was observed in vivo reflecting reduced AUC. There was a statistically significant difference in the amount of drug released in vitro in the presence of the polyherbal bitters p < 0.05. At 30 minutes time interval, a 5% difference in release of Atazanavir was observed, at the 60 minutes a 12% difference in Atazanavir release. There was also a greater reduction in Atazanavir release in pH 6.8(fed) than in 1.2 (fasted). There was a significant decrease in ALT and AST (P<0.02) in both the high dose and low dose. Photomicrographs of the liver showed evidence of enlarged nuclei and degenerated hepatocytes in the high dose group treated with Atazanavir (Figure 1). There was a strong indication that the contents of the herbal preparation contained strong heart muscle degenerating substances, which could lead to vascular eruption as shown in Figure 2 where the use of ATAZANAVIR & GOKO® depicted mild myocyte hypertrophy. This is a critical factor especially for patients who are on antihypertensive agents with the antiretroviral and also consume these bitters indiscriminately.

Conclusion
Concomitant administration of marketed poly-herbal formulation Goko® bitters alongside PIs have adverse effect on bioavailability of the PIs and may cause severe adverse effects. In Nigeria, traditional herbal medicines are often used as primary treatment for HIV/AIDS and for HIV related problems including dermatological disorders, nausea, depression, insomnia and weakness, thus, the need for enlightenment to dissuade patients from using orthodox medicines concomitantly with herbal drugs.