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Subject: Application of ATRIPLA, one tablet once daily fixed dose antiretroviral combination of efavirenz, emtricitabine, and tenofovir disproxil fumarate on the WHO model list of Essential Medicines

Dear Dr. Hill,

I have noted with interest the comments on the application of Merck Sharp & Dohme that have been published on the WHO website, and I am responding to some of the statements on clinical experience with the combination of these three antiretroviral drugs.

The combination of Efavirenz, emtricitabine, and tenofovir disproxil fumarate (EFV+FTC+TDF) has been widely used in clinical practice in many countries in the developed world, and this combination has been identified as preferred treatment regimen in recently published national treatment guidelines for treatment-naïve patients[1,2].

Since the application, an important clinical trial has been published that responds to the concerns raised in the comments[3]. In this randomized controlled trial (GS-01-934) with 512 study participants, the combination of EFV+FTC+TDF shows superior efficacy versus the comparator regimen of efavirenz and

[1] DHHS Panel on Antiretroviral Guidelines for adults and adolescents, a working group of the Office of AIDS Research Council *(http://AIDSinfo.nih.gov)*.
[2] British HIV Association. *HIV Medicine (2006), 7:487-503.*
[3] Pozniak et al: Tenofovir Disproxil Fumarate, Emtricitabine, and Efavirenz versus Fixed-dose Zidovudine/Lamivudine and efavirenz in Antiretroviral-naïve patients. Virologic, immunologic, and morphologic changes – A 96-week analysis. *J Acquir. Immune Defic. Syndr. Volume 43:535-540.*

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zidovudine/lamivudine (Combivir). Statistically significant differences are favoring the combination of EFV+FTC+TDF between treatment arms: virologic suppression as defined by HIV RNA levels<400 copies/ml is 75% in the EFV+FTC+TDF arm (versus 62% in the comparator arm; P=0.004), and immunologic improvement as defined by CD4 count increase is 270 cell/mm^3 (versus 237 in the comparator arm; P=0.036). In this controlled clinical trial, no patient has developed K65R mutation.

This study (GS-01-934) has been extended from 144 to 240 weeks. After completing 144 weeks of treatment with study drug (EFV+FTC+TDF or Combivir + EFV), subjects from both study groups were given the option to roll over into a protocol extension and switch their treatment regimen to ATRIPLA, dosed one tablet once daily on an empty stomach, preferably at bedtime. The last subject completed 144 weeks of treatment with study drug on 17 November 2006. A total of 286 subjects rolled over into the protocol extension and have received ATRIPLA. Early efficacy data demonstrate that there is no change in viral suppression after 12 weeks of treatment with ATRIPLA film-coated tablets:

- 99% of subjects had plasma HIV-1 RNA concentrations < 400 copies/ml at ATRIPLA baseline and after 12 weeks of ATRIPLA treatment, both overall and in each of the original treatment groups (ITT, Missing=Failure).
- 96% of subjects had plasma HIV-1 RNA concentrations < 50 copies/ml after 12 weeks of ATRIPLA treatment (95% following a switch from EFV+FTC+TDF, 97% following a switch from Combivir+EFV (ITT, Missing=Failure); values at ATRIPLA baseline were 95% overall, 94% EFV+FTC+TDF, and 97% Combivir + EFV).

Moreover, the aforementioned national guidelines acknowledge the superiority of efavirenz-containing regimens over nevirapine-containing regimens as demonstrated in series of clinical trials[4,5,6]. We believe this additional information is relevant in deciding about treatment choices, and request that the WHO Expert Committee consider these data in reviewing the request to add ATRIPLA to the Essential Medicines List.

Yours truly,

Donald de Korte, MD

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[4] Keiser P et al: Comparison of nevirapine and efavirenz-containing antiretroviral regimens in antiretroviral-naïve patients: a cohort study. *HIV Clin.Trial 2002; 3(4): 296-303.*

[5] Matthews G et al: Virologic suppression at 6 months is related to choice of initial regimen in antiretroviral-naïve patients: a cohort study. *AIDS 2002, 16:53-61*

[6] Cozzi-Lepri A et al: Virologic and immunologic response to regimens containing nevirapine or efavirenz in combination with 2 nucleoside analogues in the Italian Cohort Naïve Antiretrovirals (ICONA) study. *J Inf Dis 2002; 185:1062-9*