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Generic Fixed-dose Combination Antiretroviral Treatment in Resource-poor Settings: Multi-centric Observational Cohort

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Background: The use of fixed-dose combination (FDC) is a critical tool in improving highly active antiretroviral therapy (HAART). Studies on the effectiveness of combined lamivudine, stavudine and nevirapine (3TC/d4T/NVP) are scarce.

Objective: To analyse 6,861 patients in a large observational cohort from 21 Medecins Sans Frontieres (MSF) HIV/AIDS programmes taking 3TC/d4T/NVP, with subcohort analyses of patients at 12 and 18 months of treatment.

Methods: Survival was analysed using Kaplan-Meier method and factors associated with progression to death with Cox proportional hazard ratio.

Results: The median baseline CD4 cell count at initiating of FDC was 89 cells/ μ l [interquartile range (IQR), 33-158]. The median follow-up time was 4.1 months (IQR, 1.9-7.3). The incidence rate of death during follow-up was 14.2/100 person-years [95% confidence interval (CI), 13.8-14.5]. Estimates of survival (excluding those lost to follow-up) were 0.93 (95% CI, 92-94) at 6 months (n = 2,231) and 0.90 (95%

CI, 89-91) at 12 months (n = 472). Using a Cox model, the following factors were associated with death: male gender, symptomatic infection, body mass index of < 18 kg/m² and CD4 cell count of 15-50 cells/ μ l or < 15 cells/ μ l. Subcohort analysis of 655 patients after 1 year of follow-up (M12 FDC cohort) revealed that 77 percent remained on HAART and 91 percent of these still remained on the FDC regimen; 5 percent discontinued the FDC because of drug intolerance. At 18 months, 77 percent of the patients remained on HAART.

Conclusion: Positive outcomes for d4T/3TC/NVP are reported for up to 18 months in terms of efficacy and safety.

Comments: Potent, safe, inexpensive, FDC antiretroviral pill (3TC/d4T/NVP) has been used for the treatment of AIDS in many resource-poor settings including Thailand. World Health Organization (WHO) has promoted a HAART containing two nucleoside reverse transcriptase inhibitors (NRTIs) plus one nonnucleoside reverse transcriptase inhibitor (NNRTI) as an initial regimen for resource-poor settings. This study assessed the efficacy and safety of generic d4T/3TC/NVP fixed-dose combination among patients receiving treatment through Doctors Without Borders in resource-poor countries. Six thousand eight hundred and sixty-one patients in resource-poor settings who initiated FDC between October 2001 and March 2004 [Africa: 5,175 (75.4%), Asia: 1,617 (23.6%), and Central America: 69 (1.0%)] were included in the analysis. All patients required to have symptomatic disease (WHO clinical stage III-IV) and/or CD4 cell count of < 200 cells/ μ l to receive the

treatment. Selected clinical, biological, and therapeutic follow-up data were routinely obtained for all patients. Endpoints included deaths, change in CD4 cell count from baseline, and safety.

Clinical outcomes after median follow-up of 4.1 months were 413 deaths (69% of deaths occurred within the first 3 months of treatment), 328 lost to follow-up (4.8%), 128 stopped HAART (1.9%), and 5,992 were still on HAART (87.3%). Immunological outcomes showed the progressive increase in CD4 cell count, observed over time (average of 102 cells/ μl for 6 months, 144 cells/ μl for 12 months, and 173 cells/ μl for 18 months).

Overall incidence of death was 14.2/100 person-years [95% CI, 13.8-14.5]. Estimated survival rate significantly improved with higher baseline CD4 cell count ($p < 0.0001$). Several baseline factors including male sex, WHO stage IV, body mass index of $< 18 \text{ kg/m}^2$, CD4 cell count of $< 15 \text{ cells}/\mu\text{l}$, and hemoglobin of $< 8 \text{ g/dL}$ were

significantly associated with death, according to the multivariate analysis.

Subcohort analysis of treatment-naive patients (655 patients in 12 months) found similar outcomes to those of total cohort. No death attributed to an adverse event was observed. Fifty-two (8%) patients in 12-month cohort had to discontinue FDC because of grade 3/4 drug toxicity (5%), initiation of rifampicin antituberculosis treatment (2%), and unknown reason (1%).

This study has confirmed the efficacy and safety of FDC (3TC/d4T/NVP) in the treatment of AIDS patients in resource-poor settings. The clinical and immunological outcomes were significantly improved during FDC treatment in this article even though there was no virological outcome data on the cohort. The other interesting issue is the durability of the FDC in clinical practice setting. Follow-up data on this cohort will give us the important data in the management of AIDS in the resource-limited settings.