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Number of citations selected for this issue: **14**

Citation format (by alphabetical order of the authors): Author(s). **Title**. Source. **Abstr.** or **Introduction** (Authors' text) or **Notes** (selection from the paper) **Author address**, if available, **Free full text**, if available

Behets F, Matendo R, Vaz LME, Kilese N, Nanlele D, Kokolomami J, Okitolando EW, Van Rie A. **Preventing vertical transmission of HIV in Kinshasa, Democratic Republic of the Congo: a baseline survey of 18 antenatal clinics.** Bull World Health Organ 2006;84(12):969-975.

Abstr. Objective. To assess the content and delivery of essential antenatal services before implementation of programmes for prevention of mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV). Methods. We assessed 18 antenatal care centres (eight public units and ten managed by nongovernmental organizations) in Kinshasa, Democratic Republic of the Congo. We used a survey to capture information about the number and type of antenatal health workers, infrastructure capacity and the delivery of basic antenatal care services such as: nutritional counselling; tetanus toxoid vaccination; prevention and management of anaemia, malaria, sexually transmitted infections, and tuberculosis; and counselling for postpartum contraception. Findings. Antenatal care units differed with respect to size, capacity, cost, service delivery systems and content. For instance, 17 of the 18 sites offered anaemia screening but only two sites included the cost in the card that gives access to antenatal care. Nine of the clinics (50%) reported providing the malaria prophylaxis sulfadoxine pyrimethamine as per national policy, Four (22%) of the sites offered syphilis screening. Conclusion. Scaling up PMTCT programmes in under-resourced settings requires evaluation and strengthening of existing basic antenatal care service delivery.

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Free Full Text: <http://www.who.int/bulletin/volumes/84/12/05-028217.pdf>

Danel C, Peytavin G, Moh R, Konan R, Gabillard D, Anglaret X. **Stability of ritonavir soft capsule formulation in patients with and without a refrigerator at home in Côte d'Ivoire [Letter].** Int J STD AIDS 2006;17(11):784-785.

Notes. We followed 70 HIV-infected adults receiving a PI/r-containing HAART in Abidjan, Côte d'Ivoire, where the annual median temperature is 29°C. We report here data on ritonavir quantity in unused capsules that patients returned to the study centre pharmacy one month after they started HAART. To our knowledge, this is the first report on ritonavir stability in field storage conditions in sub-Saharan Africa. In a working class area of a tropical city where 67% of patients had no refrigerator at home: (i) the ritonavir quantity in 100 mg capsules which were returned after one month at home was in general reasonable (first quartile 88 mg, median 93 mg), although 24% of capsules had an abnormal external aspect; (ii) the mean ritonavir quantity was 6% lower in capsules from patients with no refrigerator at home. Preserving ritonavir at home is feasible in tropical settings, even in populations with low rate of refrigerator at home. Patients with no refrigerator who are prescribed ritonavir should be helped to find alternative modes of refrigerated conservation. In our centre, we now distribute cool boxes to these patients.

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Djomand G, Duerr A, Faulhaber JC, Struchiner CJ, Pacheco AG, Barroso PF, Melo MF, Schechter M. **Viral load and CD4 count dynamics after HIV-1 seroconversion in homosexual and bisexual men in Rio de Janeiro, Brazil.** J Acquir Immune Defic Syndrom 2006;43(4):401-404.

Abstr. Purpose: Reliable predictors of HIV disease progression are scarce in developing countries, where most HIV infections occur. We describe early virologic and immunologic events among men who have sex with men in Rio de Janeiro, Brazil. Methods: Seroconverters from 2 high-risk cohorts were followed for up to 36 months with periodic laboratory evaluations, plasma viral load, and CD4 count assessments. Viral load and CD4 count mean trajectories were computed. For the modeled viral loads, mean and median values were 24,480 (4.36 log(10)) and 19,720 (4.29 log(10)) copies/mL (range 14,880-58,090), respectively Median CD4 count was 373 cells/ μ L (range 260-508).

Overall variation on viral loads ranged from 4.3 to 5.2 log(10) copies/mL with a visible increase in the viral load starting at approximately 600 days (n = 12) after estimated time of seroconversion. The initial period of HIV infection was characterized by an increase in CD4 count (n = 29) followed by a steep decline starting at approximately 200 days (508 cells, 95% CI: 425 to 569). A gradual decrease was observed in the median CD4 count thereafter, reaching 281 (95% CI: 100 to 466) at 1000 days after the estimated date of seroconversion. Conclusions: Although viral load dynamics resembled those observed in developed countries, CD4 counts seem to decline at a faster rate than in the Multicenter AIDS Cohort Study (MACS) cohort. Clinical and survival data are needed to assess the impact of interventions, such as antiretroviral therapy, on the clinical course of HIV infection in Brazil.

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El Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, Babiker A, Burman W, Clumeck N, Cohen CJ, Cohn D, Cooper D, Darbyshire J, Emery S, Fatkenheuer G, Gazzard B, Grund B, Hoy J, Klingman K, Losso M, Mejia JMR, Markowitz N, Neuhaus J, Phillips A, Rappoport C. **CD4+count-guided interruption of antiretroviral treatment.** N Engl J Med 2006;355(22):2283-2296.

Abstr. BACKGROUND: Despite declines in morbidity and mortality with the use of combination antiretroviral therapy, its effectiveness is limited by adverse events, problems with adherence, and resistance of the human immunodeficiency virus (HIV). METHODS: We randomly assigned persons infected with HIV who had a CD4+ cell count of more than 350 per cubic millimeter to the continuous use of antiretroviral therapy (the viral suppression group) or the episodic use of antiretroviral therapy (the drug conservation group). Episodic use involved the deferral of therapy until the CD4+ count decreased to less than 250 per cubic millimeter and then the use of therapy until the CD4+ count increased to more than 350 per cubic millimeter. The primary end point was the development of an opportunistic disease or death from any cause. An important secondary end point was major cardiovascular, renal, or hepatic disease. RESULTS: A total of 5472 participants (2720 assigned to drug conservation and 2752 to viral suppression) were followed for an average of 16 months before the protocol was modified for the drug conservation group. At baseline, the median and nadir CD4+ counts were 597 per cubic millimeter and 250 per cubic millimeter, respectively, and 71.7% of participants had plasma HIV RNA levels of 400 copies or less per milliliter. Opportunistic disease or death from any cause occurred in 120 participants (3.3 events per 100 person-years) in the drug conservation group and 47 participants (1.3 per 100 person-years) in the viral suppression group (hazard ratio for the drug conservation group vs. the viral suppression group, 2.6; 95% confidence interval [CI], 1.9 to 3.7; P<0.001). Hazard ratios for death from any cause and for major cardiovascular, renal, and hepatic disease were 1.8 (95% CI, 1.2 to 2.9; P=0.007) and 1.7 (95% CI, 1.1 to 2.5; P=0.009), respectively. Adjustment for the latest CD4+ count and HIV RNA level (as time-updated covariates) reduced the hazard ratio for the primary end point from 2.6 to 1.5 (95% CI, 1.0 to 2.1). CONCLUSIONS: Episodic antiretroviral therapy guided by the CD4+ count, as used in our study, significantly increased the risk of opportunistic disease or death from any cause, as compared with continuous antiretroviral therapy, largely as a consequence of lowering the CD4+ cell count and increasing the viral load. Episodic antiretroviral therapy does not reduce the risk of adverse events that have been associated with antiretroviral therapy.

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Giaquinto C, Rampon O, De Rossi A. **Antiretroviral therapy for prevention of mother-to-child HIV transmission - Focus on single-dose nevirapine.** Clin Drug Invest 2006;26 (11):611-627.

Abstr. Administration of potent antiretroviral combination therapy in the second and third trimester of pregnancy and during delivery, and for 6 weeks postpartum to the infant, may reduce HIV transmission from the mother to the child to < 2% in formula-fed infants. In resource-constrained settings where women have limited access to antenatal care, use of shorter and more practical regimens, including nucleoside reverse transcriptase inhibitors (NRTIs) and/or non-NRTIs (NNRTIs) commenced later in pregnancy, has demonstrated efficacies ranging from 18% to 70% in breast- and bottle-fed populations. Because shorter interventions include regimens such as single-dose nevirapine or zidovudine monotherapy, which do not provide maximal suppression of viral replication, emergence of resistant mutations in mother and infant occurs frequently, primarily after exposure to drugs with low genetic barriers (i.e. those requiring only one genotypic mutation to develop resistance), such as nevirapine. Different studies have reported nevirapine resistance rates ranging from 25% to 69% in mothers receiving single-dose nevirapine alone. Because NNRTI-based combinations of antiretroviral agents are recommended as first-line therapy in countries where single-dose nevirapine is the main option for preventing mother-to-child transmission of HIV, concerns have been raised as to whether single-dose nevirapine prophylaxis can compromise the efficacy of subsequent NNRTI-based antiretroviral therapy regimens. However, although some studies have shown that nevirapine exposure may impact on short-term virological outcome, the clinical relevance of nevirapine resistance remains unclear, especially in women who start treatment > 6 months after delivery or in those who are not severely immunocompromised. Furthermore, studies have shown that adding short-course (up to 7 days) zidovudine or zidovudine/lamivudine prophylaxis after delivery may dramatically reduce the occurrence of nevirapine resistance in both mothers and infants. Until data are available that allow a better understanding of the relevance of antiretroviral drug resistance acquired as a result of mother-to-child HIV transmission prophylaxis, women and children who have previously received single-dose nevirapine as part of a mother-to-child transmission prevention strategy should be considered eligible for NNRTI-based regimens and should not be denied access to antiretroviral therapy.

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Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S. **Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy.** J Infection 2006;53(6):357-363.

Abstr. Objective: To determine the frequency, risk factors and mortality rate of immune reconstitution inflammatory syndrome (IRIS) of tuberculosis (TB) in patients co-infected with HIV/TB and receiving antiretroviral therapy (ART). Methods: A retrospective study was conducted in Bamrasnaradura Infectious Diseases Institute and Ramathibodi Hospital, Thailand. Results: There were 167 patients with a mean age of 34.5 years. Median (IQR) CD4 cell counts was 36 (15-69) cells/mm³ and median (IQR) HIV RNA was 427,000 (189,000-750,000) copies/ml. ART was initiated at a median (IQR) duration of 2.2 (1.4-3.7) months after TB treatment. IRIS was identified in 21 (12.6%) patients. Patients with IRIS had a higher proportion of extrapulmonary TB than patients without IRIS (P < 0.001). By multivariate analysis, extrapulmonary TB was a risk factor for IRIS (odds ratio = 8.225, 95% confidence interval = 1.785-37.911, P = 0.007). Of 21 patients with IRIS, 15 patients developed IRIS within the first two months of ART. The mortality rate in patients with and without IRIS was not different (9.5% versus 2.1%, P = 0.119). Conclusions: The rate of TB IRIS is 13% in patients co-infected with HIV and TB. Extrapulmonary TB is a risk factor for IRIS. Closely monitored clinical care in the first few months of ART initiation and further interventional studies to minimize mortality of TB IRIS are needed.

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Manosuthi W, Ruxrungtham K, LikAnonsakul S, Prasithsirikul W, Inthong Y, Phoorisri T, Sungkanuparph S. **Nevirapine levels after discontinuation of rifampicin therapy and 60-week efficacy of nevirapine-based antiretroviral therapy in HIV-infected patients with tuberculosis.** Clin Infect Dis 2007;44(1):141-144.

Abstr. Seventy patients with human immunodeficiency virus (HIV) and tuberculosis coinfection who initiated nevirapine-based antiretroviral therapy and had trough nevirapine levels determined while receiving rifampicin were enrolled in a study. After discontinuation of rifampicin therapy, mean nevirapine levels (+/- standard deviation) increased from 5.4 +/- 3.5mg/L to 6.4 +/- 3.4mg/L (P =.047), but no nevirapine-related adverse events occurred. There was no statistically significant difference in 60-week antiviral efficacy between these patients and patients receiving nevirapine-based antiretroviral therapy alone (P >.05).

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Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, Wu P, Wilson K, Buchan I, Gill CJ, Cooper C. **Adherence to HAART: A systematic review of developed and developing nation patient-reported barriers and facilitators - art. no. e438.** Plos Med 2006;3(11):NIL_71-NIL_96.

Abstr. Background Adherence to highly active antiretroviral therapy (HAART) medication is the greatest patient-enabled predictor of treatment success and mortality for those who have access to drugs. We systematically reviewed the literature to determine patient-reported barriers and facilitators to adhering to antiretroviral therapy. Methods and Findings We examined both developed and developing nations. We searched the following databases: AMED (inception to June 2005), Campbell Collaboration (inception to June 2005), CinAhl (inception to June 2005), Cochrane Library (inception to June 2005), Embase (inception to June 2005), ERIC (inception to June 2005), MedLine (inception to June 2005), and NHS EED (inception to June 2005). We retrieved studies conducted in both developed and developing nation settings that examined barriers and facilitators addressing adherence. Both qualitative and quantitative studies were included. We independently, in duplicate, extracted data reported in qualitative studies addressing adherence. We then examined all quantitative studies addressing barriers and facilitators noted from the qualitative studies. In order to place the findings of the qualitative studies in a generalizable context, we meta-analyzed the surveys to determine a best estimate of the overall prevalence of issues. We included 37 qualitative studies and 47 studies using a quantitative methodology (surveys). Seventy-two studies (35 qualitative) were conducted in developed nations, while the remaining 12 (two qualitative) were conducted in developing nations. Important barriers reported in both economic settings included fear of disclosure, concomitant substance abuse, forgetfulness, suspicions of treatment, regimens that are too complicated, number of pills required, decreased quality of life, work and family responsibilities, falling asleep, and access to medication. Important facilitators reported by patients in developed nation settings included having a sense of self-worth, seeing positive effects of antiretrovirals, accepting their seropositivity, understanding the need for strict adherence, making use of reminder tools, and having a simple regimen. Among 37 separate meta-analyses examining the generalizability of these findings, we found large heterogeneity. Conclusions We found that important barriers to adherence are consistent across multiple settings and countries. Research is urgently needed to determine patient-important factors for adherence in developing world settings. Clinicians should use this information to engage in open discussion with patients to promote adherence and identify barriers and facilitators within their own populations.

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Moore DM, Mermin J, Awor A, Yip B, Hogg RS, Montaner JSG. **Performance of immunologic responses in predicting viral load suppression - Implications for monitoring patients in resource-limited settings.** J Acquir Immune Defic Syndrom 2006;43(4):436-439.

Abstr. Background: World Health Organization (WHO) guidelines for the use of antiretroviral therapy (ART) in resource-limited settings state that CD4 cell counts may be used to indicate when ART regimens should be changed because of treatment failure. The performance of immunologic monitoring for this purpose has not been evaluated, however. Methods: Participants aged 18 years from the British Columbia HIV/AIDS Drug Treatment Program who had CD4 cell counts \leq 200 cells/ μ L or an AIDS diagnosis at baseline had CD4 cell counts measured at 6 and 12 months after treatment initiation. Logistic regression analysis was used to calculate sensitivity, specificity, and positive and negative predictive values for immunologic responses in terms of predicting failure to achieve 2 viral load measurements $<$ 500 copies/mL within 1 year. Results: Viral load suppression occurred in 674 (60%) of 1125 subjects. Using no increase in CD4 cell counts at 6 months as a definition of treatment failure had a sensitivity of 34%, specificity of 94%, positive predictive value of 75%, and negative predictive value of 71% for predicting failure to achieve virologic suppression. Using 12-month CD4 cell count values, the measurements were 35%, 95%, 79%, and 73%, respectively. Conclusion: immunologic criteria to predict which patients have not achieved virologic suppression results in significant misclassification of therapeutic responses.

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Nyandiko WM, Ayaya S, Nabakwe E, Tenge C, Sidle JE, Yiannoutsos CT, Musick B, Wools Kaloustian K, Tierney WM. **Outcomes of HIV-infected orphaned and non-orphaned children on antiretroviral therapy in western Kenya.** J Acquir Immune Defic Syndrom 2006;43(4):418-425.

Abstr. Objectives: Determine outcome differences between orphaned and non-orphaned children receiving antiretroviral therapy (ART). Design: Retrospective review of prospectively recorded electronic data. Setting: Nine HIV clinics in western Kenya Population: 279 children on ART enrolled between August 2002 and February 2005. Main Measures: Orphan status, CD4%, sex- and age-adjusted height (HAZ) and weight (WAZ) z scores, ART adherence, mortality. Results: Median follow-up was 34 months. Cohort included 51% males and 54% orphans. At ART initiation (baseline), 71% of children had CDC clinical stage B or C disease. Median CD4% was 9% and increased dramatically the first 30 weeks of therapy, then leveled off. Parents and guardians reported perfect adherence at every visit for 75% of children. Adherence and orphan status were not significantly associated with CD4% response. Adjusted for baseline age, follow-up was significantly shorter among orphaned children (median 33 vs. 41 weeks, $P = 0.096$). One-year mortality was 7.1% for orphaned and 6.6% for non-orphaned children ($P = 0.836$). HAZ and WA-Z were significantly below norm in both groups. With ART, HAZ remained stable, while WAZ tended to increase toward the norm, especially among non-orphans. Orphans showed identical weight gains as non-orphans the first 70 weeks after start of ART but experienced reductions afterwards. Conclusions: Good ART adherence is possible in western rural Kenya. ART for HIV-infected children produced substantial and sustainable CD4% improvement. Orphan status was not associated with worse short-term outcomes but may be a factor for long-term therapy response. ART alone may not be sufficient to reverse significant developmental lags in the HIV-positive pediatric population.

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Simoni JM, Pearson CR, Pantalone DW, Marks G, Crepaz N. **Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load - A meta-analytic review of randomized controlled trials.** J Acquir Immune Defic Syndrom 2006;43 Suppl. 1:S23-S35.

Abstr. Adherence to highly active antiretroviral therapy (HAART) is generally suboptimal, limiting the effectiveness of HAART. This meta-analytic review examined whether behavioral interventions addressing HAART adherence are successful in increasing the likelihood of a patient attaining 95% adherence or an undetectable HIV-1 RNA viral load (VL). We searched electronic databases from January 1996 to September 2005, consulted with experts in the field, and hand searched reference sections from relevant articles. Nineteen studies (with a total of 1839 participants) met the selection criteria of describing a randomized controlled trial among adults evaluating a behavioral intervention with HAART adherence or VL as an outcome. Random-effects models indicated that across studies, participants in the intervention arm were more likely than those in the control arm to achieve 95% adherence (odds ratio [OR]=1.50, 95% confidence interval [CI]: 1.16 to 1.94); the effect was nearly significant for undetectable VL (OR=1.25; 95% CI: 0.99 to 1.59). The intervention effect for 95% adherence was significantly stronger in studies that used recall periods of 2 weeks or 1 month (vs. \leq 7 days). No other stratification variables (ie, study, sample, measurement, methodologic quality, intervention characteristics) moderated the intervention effect, but some potentially important factors were observed. In sum, various HAART adherence intervention strategies were shown to be successful, but more research is needed to identify the most efficacious intervention components and the best methods for implementing them in real-world settings with limited resources.

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Thistle P, Spitzer RF, Glazier RH, Pilon R, Arbess G, Simor A, Boyle E, Chitsike I, Chipato T, Gottesman M, Silverman M. **A randomized, double-blind, placebo-controlled trial of combined nevirapine and zidovudine compared with nevirapine alone in the prevention of perinatal transmission of HIV in Zimbabwe.** Clin Infect Dis 2007;44(1):111-119.

Abstr. Background. A single dose of nevirapine (sdNVP) administered to both mother and infant can decrease mother-to-child transmission of human immunodeficiency virus (HIV) by 47%, compared with ultra-short course zidovudine therapy (usZDV). There is limited data about the benefit of usZDV added to sdNVP to prevent mother-to-child transmission. Methods. We performed a double-blind, randomized, placebo-controlled trial to determine whether usZDV combined with sdNVP improved neonatal outcome, compared with sdNVP alone. Mothers were randomized to 1 of 2 treatment groups. Mothers in the usZDV/sdNVP group received a loading dose of zidovudine (600 mg administered orally) and continued to receive 300-mg doses of zidovudine orally every 3 h while in labor, and their infants received zidovudine at a dosage of 2 mg per kg of body weight 4 times per day orally for 72 h. Mothers and infants in the sdNVP group received zidovudine placebo dosed in the same manner. All mothers also received nevirapine at a dosage of 200 mg orally while in labor, and all infants received nevirapine 2 mg per kg of body weight orally within 72 h of delivery. Results. The study was stopped on the basis of futility, because interim data showed that, at present trends, superiority would not be demonstrated. Results at 6 weeks of age were available for 609 infants. The primary end point of HIV RNA positivity or death occurred in 21.8% of infants in the usZDV/sdNVP arm and 23.6% of the infants in the sdNVP arm. Conclusion. usZDV, when added to a standard 2-dose regimen of sdNVP, did not demonstrate a clinically important decrease in the combined end point of mother-to-child transmission or infant death. High rates of adverse maternal and infant outcome in both study arms suggest that improved approaches are necessary.

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Williams AB, Friedland GH. **Enhancing adherence: Proceedings of the State of the Science Meeting on Intervention Research to Improve ARV adherence - Introduction.** J Acquir Immune Defic Syndrom 2006;43 Suppl. 1:S1-S2.

Abstr. With the advent of effective combinations of antiretroviral agents in 1996, the crucial importance of patient adherence to medication regimens rapidly became apparent. In response, HIV/AIDS clinical and behavioral researchers launched major research projects aimed at describing the levels and determinants of adherence. In recent years, the percent of prescribed doses taken has been linked consistently to biologic treatment outcomes, including the development of resistance to antiretroviral medications, and to clinical outcomes as well. Unfortunately, it has also become clear that few patients are able to maintain a medication adherence rate of 90%, which is the most likely minimum necessary for successful virologic suppression in the greatest proportion of patients, thus forestalling the development of drug-resistant virus and eventual clinical failure.

The articles in this special supplement comprise discussions of the theoretic underpinnings of adherence research and of the challenges of collaboration across disciplines (see the articles by Friedland, Fisher et al, and Ware et al), a state-of-the-art review of the outcomes of adherence intervention trials (see the articles by Simoni et al and Gordon), results from 2 adherence intervention clinical trials (see the articles by Mannheimer et al and Smith-Rohrberg et al), explorations of important methodologic aspects of adherence intervention research such as the role of qualitative methods (see the article by Sankar et al), the challenge of developing a theory-driven intervention (see the article by Remien et al), measurement strategies (see the article by Berg and Arnsten), data management issues with electronic monitoring devices (see the article by Fennie et al), an innovative approach to assess intervention effectiveness (see the article by Petersen et al), a promising cost-effectiveness model for adherence interventions (see the article by Freedberg et al), and the earliest reports of exciting work being conducted abroad in the resource-limited parts of the world in which the epidemic continues to expand (see the articles by Maneesriwongul et al, Nachega et al, Mukherjee et al, Wong et al, and Pearson et al). Finally, Margaret Chesney, one of the early leaders in antiretroviral adherence research, comments on where we are today and offers her thoughts for the future.

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Zhou ML, Phanupak P, Kiertiburanakul S, Ditangco R, Kamarulzaman A, Pujary S. **Highly active antiretroviral treatment containing efavirenz or nevirapine and related toxicity in the TREAT Asia HIV Observational Database.** J Acquir Immune Defic Syndr 2006;43(4):501-503.

Abstr. The World Health Organisation recommends the use of first-line therapy with two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-NRTI (NNRTI), either efavirenz (EFV) or nevirapine (NVP), in the management of HIV in resource-limited countries. Studies have shown highly active antiretroviral therapy (HAART) regimens that include an NNRTI are effective and well tolerated, but adverse events, such as hypersensitivity reaction and hepatotoxicity, are relatively common. High rates of NVP-associated rash have also been reported in Thai and Chinese patients. We compared between ethnicities the rates of skin rash and hepatotoxicity in patients from TREAT Asia HIV Observational Database (TAHOD) receiving EFV- or NVP-containing HAART that led to discontinuation of EFV or NVP. Analyses included 735 and 813 patients who started EFV- and NVP- containing HAART, respectively. In TAHOD, we observed a high rate of NVP discontinuation due to rash in Thai and especially Filipino patients. Whether this reflects ethnic differences or local site monitoring differences is unclear.

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