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Ananworanich J, Gayet Ageron A, Le Braz M, Prasithsirikul W, Chetchotisakd P, Kiertiburanakul S, et al. **CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial.** *Lancet* 2006;368(9534):459-465.

Abstr. Background Stopping antiretroviral therapy in patients with HIV-1 infection can reduce costs and side-effects, but carries the risk of increased immune suppression and emergence of resistance. Methods 430 patients with CD4-positive T-lymphocyte (CD4) counts greater than 350 cells per μ L, and viral load less than 50 copies per mL were randomised to continued therapy (n=146) or scheduled treatment interruptions (n=284). Median time on randomised treatment was 21.9 months (range 16.4-25.3). Primary endpoints were proportion of patients with viral load less than 50 copies per mL at the end of the trial, and amount of drugs used. Analysis was intention-to-treat. This study is registered at ClinicalTrials.gov with the identifier NCT00113126. Findings Drug savings in the scheduled treatment interruption group, compared with continuous treatment, amounted to 61.5%. 257 of 284 (90.5%) patients in the scheduled treatment interruption group reached a viral load less than 50 copies per mL, compared with 134 of 146 (91.8%) in the continued treatment group (difference 1.3%, 95% CI-4.3 to 6.9, p=0.90). No AIDS-defining events occurred. Diarrhoea and neuropathy were more frequent with continuous treatment; candidiasis was more frequent with scheduled treatment interruption. Ten patients (2.3%) had resistance mutations, with no significant differences between groups. Interpretation Drug savings with scheduled treatment interruption were substantial, and no evidence of increased treatment resistance emerged. Treatment-related adverse events were more frequent with continuous treatment, but low CD4 counts and minor manifestations of HIV infection were more frequent with scheduled treatment interruption.

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Bisson GP, Frank I, Gross R, Lo Re V, Strom JB, Wang XM, Mogorosi M, Gaolathe T, Ndwapi N, Friedman H, Strom BL, Dickinson D. **Out-of-pocket costs of HAART limit HIV treatment responses in Botswana's private sector.** *AIDS* 2006;20(9):1333-1336.

Abstr. A large number of HIV-infected patients in sub-Saharan Africa pay out-of-pocket for HAART. This analysis from Botswana indicates that higher median out-of-pocket regimen costs to patients for the initial 30 days of HAART are associated with failure to achieve a viral load < 400 copies/ml [US\$32; interquartile range (IQR), 20-84 compared with US\$22; (IQR, 17-36), P = 0.001]. HAART costs should be minimized as scale-up efforts in sub-Saharan Africa progress.

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Bonnet MMB, Pinoges LLP, Varaine FFV, Oberhauser BBO, DDO OB, Kebede YYK, Hewison CCH, Zachariah RRZ, Ferradini LLF. **Tuberculosis after HAART initiation in HIV-positive patients from five countries with a high tuberculosis burden.** *AIDS* 2006;20(9):1275-1279.

Abstr. Background: HAART reduces tuberculosis (TB) incidence in people living with HIV/AIDS but those starting HAART may develop active TB or subclinical TB may become apparent in the immune reconstitution inflammatory syndrome. Objective: To measure the incidence rate of notified TB in people receiving HAART in five HIV programmes occurring in low-resource countries with a high TB/HIV burden. Methods: A retrospective review in five Medecins Sans Frontieres programmes (Cambodia, Thailand, Kenya, Malawi and Cameroon) allowed incidence rates of notified TB to be calculated based on follow-up time after HAART initiation. Results: Among 3151 patients analysed, 90% had a CD4 cell count of < 200 cells/ μ l. Median follow-up time ranged from 3.7 months in Thailand or Kenya to 11.1 months in Cambodia. Incidence rates were 7.6, 10.4, 17.6, 14.3 and 4.8/100 person-years for pulmonary TB and 12.7, 4.3, 6.9, 2.1 and 0/100 person-years for extra-pulmonary TB in the programmes in Cambodia, Thailand, Kenya, Malawi and Cameroon, respectively. Overall, 62.3% of pulmonary TB and 54.9% of extra-pulmonary TB were diagnosed within 3 months after HAART initiation. Conclusion: High incidence rates of notified TB under HAART in programmes held in poor-resource countries were observed; these were likely to include both undiagnosed prevalent TB at HAART initiation and subclinical TB developing during the immune reconstitution inflammatory syndrome. This raises operational issues concerning TB diagnosis and treatment of TB/HIV-coinfected patients and prompts for urgent TB and HIV care integration..

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Eshleman SH, Church JD, Shu C, Guay LA, Mwatha A, Fiscus SA, Mmiro F, Musoke P, Kumwenda N, Jackson JB, Taha TE, Hoover DR. **Comparison of HIV-1 mother-to-child transmission after single-dose nevirapine prophylaxis among African women with subtypes A, C, and D [Letter to the Editor]**. Journal of Acquired Immune Deficiency Syndromes 2006;42(4):518-521.

Introduction. The HIVNET 012 trial in Uganda showed that mother-to-child transmission (MTCT) of HIV-1 can be prevented by providing pregnant women and their infants with a single dose (SD) of the antiretroviral drug, nevirapine (NVP). Safety and efficacy of 1- or 2-dose NVP prophylaxis for prevention of MTCT have been documented in other studies. We have shown that NVP resistance emerges in some women after SD NVP prophylaxis and that the portion of women with NVP resistance is influenced by HIV-1 subtype. At 6 to 8 weeks after SD NVP, NVP resistance was more common in women with subtype C (69.2%) than in women with subtype D (36.1%, $P < 0.0001$) or subtype A (19.4%, $P < 0.0001$). Selection of NVP-resistant HIV-1 variants in women after NVP dosing could theoretically lower the efficacy of NVP prophylaxis for prevention of HIV transmission by breast-feeding in the first few weeks after birth. In the HIVNET 012 trial, most women were infected with HIV-1 subtype A or D. Risk of MTCT was slightly (but not statistically) higher in women with subtype D. In this report, we combined data from the HIVNET 012 and NVAZ trials to compare the risk of MTCT in women with subtype C to the risk of MTCT in women with subtypes A and D in the setting of SD NVP prophylaxis.

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Filler SJ, Kazembe P, Thigpen M, Macheso A, Parise ME, Newman RD, Steketee RW, Hamel M. **Randomized trial of 2-dose versus monthly sulfadoxine-pyrimethamine intermittent preventive treatment for malaria in HIV-positive and HIV-negative pregnant women in Malawi**. Journal of Infectious Diseases 2006;194(3):286-293.

Abstr. Background. Intermittent preventive treatment during pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) decreases placental malaria parasitemia and associated maternal anemia, premature delivery, and low birth weight. However, the optimal regimen in the setting of a high prevalence of human immunodeficiency virus (HIV) infection remains unclear. Methods. In Malawi, where the efficacy of SP for the treatment of malaria in children is decreasing, we conducted a randomized, nonblinded study to compare the efficacy of monthly SP IPTp with a 2-dose regimen for the prevention of placental parasitemia in HIV-positive and -negative primigravid and secundigravid women. Results. Of HIV-positive women, 7.8% who received monthly SP had placental malaria, compared with 21.5% of those who received 2-dose SP (relative risk [RR], 0.36 [95% confidence interval {CI}, 0.17-0.79]). Of HIV-negative women, 2.3% who received monthly SP and 6.3% who received 2-dose SP had placental malaria (RR, 0.37 [95% CI, 0.11-1.19]). Less than 1% of women reported adverse drug reactions, with no increase in HIV-positive women or those who received monthly SP. Conclusions. In HIV-positive pregnant women, monthly SP IPTp is more efficacious than a 2-dose regimen in preventing placental malaria. The study also demonstrates the continued efficacy of SP for the prevention of placental malaria, even in the face of its decreasing efficacy for the treatment of malaria in children. In areas with intense transmission of falciparum malaria and a high prevalence of HIV infection, monthly SP IPTp should be adopted.

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Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, Sutherland D, Vitoria M, Guerna T, De Cock K. **The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings**. Lancet 2006;368(9534):505-510.

Abstr. WHO has proposed a public-health approach to antiretroviral therapy (ART) to enable scaling-up access to treatment for HIV-positive people in developing countries, recognising that the western model of specialist physician management and advanced laboratory monitoring is not feasible in resource-poor settings. In this approach, standardised simplified treatment protocols and decentralised service delivery enable treatment to be delivered to large numbers of HIV-positive adults and children through the public and private sector. Simplified tools and approaches to clinical decision-making, centred on the "four Ss"-when to: start drug treatment; substitute for toxicity; switch after treatment failure; and stop-enable lower level health-care workers to deliver care. Simple limited formularies have driven large-scale production of fixed-dose combinations for first-line treatment for adults and lowered prices, but to ensure access to ART in the poorest countries, the care and drugs should be given free at point of service delivery. Population-based surveillance for acquired and transmitted resistance is needed to address concerns that switching regimens on the basis of clinical criteria for failure alone could lead to widespread emergence of drug-resistant virus strains. The integrated management of adult or childhood illness (IMAI/IMCI) facilitates decentralised implementation that is integrated within existing health systems. Simplified operational guidelines, tools, and training materials enable clinical teams in primary-care

and second-level facilities to deliver HIV prevention, HIV care, and ART, and to use a standardised patient-tracking system.

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Hammer SM, Saag MS, Schechter M, Montaner JSG, Schooley RT, Jacobsen DM, Thompson MA, Carpenter CCJ, Fischl MA, Gazzard BG, Gatell JM, Hirsch MS, Katzenstein DA, Richman DD, Vella S, Yeni PG, Volberding PA. **Treatment for adult HIV infection - 2006 recommendations of the International AIDS Society-USA panel.** JAMA 2006;296(7):827-843.

Abstr. Context Guidelines for antiretroviral therapy are important for clinicians worldwide given the complexity of the field and the varied clinical situations in which these agents are used. The International AIDS Society - USA panel has updated its recommendations as warranted by new developments in the field. Objective To provide physicians and other human immunodeficiency virus (HIV) clinicians with current recommendations for the use of antiretroviral therapy in HIV-infected adults in circumstances for which there is relatively unrestricted access to drugs and monitoring tools. The recommendations are centered on 4 key issues: when to start antiretroviral therapy; what to start; when to change; and what to change. Antiretroviral therapy in special circumstances is also described. Data Sources and Study Selection A 16-member noncompensated panel was appointed, based on expertise in HIV research and patient care internationally. Data published or presented at selected scientific conferences from mid 2004 through May 2006 were identified and reviewed by all members of the panel. Data Extraction and Synthesis Data that might change previous guidelines were identified and reviewed. New guidelines were drafted by a writing committee and reviewed by the entire panel. Conclusions Antiretroviral therapy in adults continues to evolve rapidly, making delivery of state-of-the-art care challenging. Initiation of therapy continues to be recommended in all symptomatic persons and in asymptomatic persons after the CD4 cell count falls below 350/ μ L and before it declines to 200/ μ L. A nonnucleoside reverse transcriptase inhibitor or a protease inhibitor boosted with low-dose ritonavir each combined with 2 nucleoside (or nucleotide) reverse transcriptase inhibitors is recommended with choice being based on the individual patient profile. Therapy should be changed when toxicity or intolerance mandate it or when treatment failure is documented. The virologic target for patients with treatment failure is now a plasma HIV-1 RNA level below 50 copies/mL. Adherence to antiretroviral therapy in the short-term and the long-term is crucial for treatment success and must be continually reinforced.

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Hausler HP, Sinanovic E, Kumaranayake L, Naidoo P, Schoeman H, Karpakis B, Godfrey Faussett P. **Costs of measures to control tuberculosis/HIV in public primary care facilities in Cape Town, South Africa.** Bulletin of the World Health Organization 2006;84(7):528-536.

Abstr. Objective To measure the costs and estimate the cost-effectiveness of the ProTEST package of tuberculosis/human immunodeficiency virus (TB/HIV) interventions in primary health care facilities in Cape Town, South Africa. Methods We collected annual cost data retrospectively using ingredients-based costing in three primary care facilities and estimated the cost per HIV infection averted and the cost per TB case prevented. Findings The range of costs per person for the ProTEST interventions in the three facilities were: US\$ 7-11 for voluntary counselling and testing (VCT), US\$ 81-166 for detecting a TB case, US\$ 92-183 for completing isoniazid preventive therapy (IPT) and US\$ 20-44 for completing six months of cotrimoxazole preventive therapy. The estimated cost per HIV infection averted by VCT was US\$ 67-112. The cost per TB case prevented by VCT (through preventing HIV) was US\$ 129-215, by intensified case finding was US\$ 323-664 and by IPT was US\$ 486-962. Sensitivity analysis showed that the use of chest X-rays for IPT screening decreases the cost-effectiveness of IPT in preventing TB cases by 36%. IPT screening with or without tuberculin purified protein derivative screening was almost equally cost-effective. Conclusion We conclude that the ProTEST package is cost saving. Despite moderate adherence, linking prevention and care interventions for TB and HIV resulted in the estimated costs of preventing TB being less than previous estimates of costs of treating it. VCT was less expensive than previously reported in Africa.

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Holmes CB, Wood R, Badri M, Zilber S, Wang BX, Maartens G, Zheng H, Lu ZG, Freedberg KA, Losina E. **CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: Implications for prophylaxis and treatment.** Journal of Acquired Immune Deficiency Syndromes 2006;42(4):464-469.

Abstr. Objectives: To determine the rate of CD4 decline and the incidence of opportunistic infections (OIs) among antiretroviral therapy-naïve South African HIV-infected patients and inform timing of OI prophylaxis. Methods: We used mixed-effect models to estimate CD4 cell decline by CD4 cell count strata in HIV-infected patients in the Cape Town AIDS Cohort between 1984 and 2000. Stratum-specific OI incidence per 100 person-

years of observation was determined using incidence density analysis. Results: Nine hundred seventy-four patients with 2 or more CD4 cell counts were included. CD4 counts declined by 47.1 cells/mu L per year in the stratum with more than 500 cells/mu L, 30.6 cells/mu L per year in the stratum with 351 to 500 cells/mu L, and 20.5 cells/mu L per year in the stratum with 201 to 350 cells/mu L. Tuberculosis and oral candidiasis were the only OIs that occurred frequently in the stratum with more than 200 CD4 cells/RL. Rates of chronic diarrhea, wasting syndrome, tuberculosis, and oral and esophageal candidiasis increased in the stratum with less than 200 cells/mu L, and rates of all OIs were highest in the stratum with 50 cells/mu L or less. Conclusions: CD4 cell count declines were dependent on CD4 strata and can inform timing of clinic visits and treatment initiation in South Africa. Incidence rates of OIs suggest that targeted OI prophylaxis could prevent substantial HIV-related morbidity in South Africa.

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Humphrey JH, Hargrove JW, Malaba LC, Iliff PJ, Moulton LH, Mutasa K, Zvandasara P, Nathoo KJ, Mzengeza F, Chidawanyika H, Zijenah LS, Ward BJ. **HIV incidence among post-partum women in Zimbabwe: risk factors and the effect of vitamin A supplementation.** AIDS 2006;20(10):1437-1446.

Abstr. Objective: To test whether post-partum vitamin A supplementation can reduce incident HIV among post-partum women and identify risk factors for HIV incidence. Design: Randomized, placebo-controlled trial. Methods: Between November 1997 and January 2001, 14110 women were randomly administered 400000 IU vitamin A or placebo within 96 h post-partum. HIV incidence was monitored among 9562 HIV-negative women. Results: Cumulative incidence was 3.4% [95% confidence interval (CI), 3.0-3.8] and 6.5% (95% CI, 5.7-7.4) over 12 and 24 months post-partum, respectively. Vitamin A supplementation had no impact on incidence [hazard ratio (HR), 1.08; 95% CI, 0.85-1.38]. However, among 398 women for whom baseline serum retinol was measured, those with levels indicative of deficiency (< 0.7 ILmol/l, 9.2% of those measured) were 10.4 (95% CI, 3.0-36.3) times more likely to seroconvert than women with higher concentrations. Furthermore, among women with low serum retinol, vitamin A supplementation tended to be protective against incidence (HR, 0.29; 95% CI, 0.03-2.60; P = 0.26), although not significantly so, perhaps due to limited statistical power. Severe anaemia (haemoglobin < 70 g/l) was associated with a 2.7-fold (95% CI, 1.2-6.1) greater incidence. Younger women were at higher risk of HIV infection: incidence declined by 5.7% (2.8-8.6) with each additional year of age. Conclusion: Among post-partum women, a single large-dose vitamin A supplementation had no effect on incidence, although low serum retinol was a risk factor for seroconversion. Further investigation is required to determine whether vitamin A supplementation of vitamin-A-deficient women or treatment of anaemic women can reduce HIV incidence.

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Kaleebu P, Pillay D, Walker AS, Robertson V, Gale CV, Enzama R, et al. **Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa** AIDS 2006;20(10):1391-1399.

Abstr. Objectives: To evaluate virologic response up to 48 weeks, and emergence of HIV-1 resistance mutations at 24 weeks, in therapy-naive adults initiating zidovudine/lamivudine/tenofovir DF. Design: A cohort within the DART trial. Methods: Plasma HIV-1 RNA was assayed in 300 adults with baseline CD4 cell count < 200 cells/mu l from sites in Uganda and Zimbabwe using the Roche Amplicor assay v1.5. Samples with HIV-1 RNA > 1000 copies/ml at 24 weeks were sequenced in the pol region. Results: Median baseline CD4 cell count was 101 cells/mu l and HIV-1 RNA 279910copies/ml (mean, 5.4 log(10)). At 48 weeks, 61% (165/272) had HIV-1 RNA < 50 and 72% (196/272) < 400 copies/ml, compared with 59% (167/281) and 79% (221/281) at 24 weeks. At 24 and 48 weeks, 15 and 24% respectively had HIV-1 RNA > 1000 copies/ml (6 and 17% > 10000 copies/ml), and mean CD4 cell count increases were 103 and 127 cells/mu l, respectively. Higher baseline CD4 cell count was the most important predictor of virological suppression at 48 weeks, with little effect of baseline viral load. Eighteen of 20 genotypes from week 24 samples with HIV-1 RNA > 1000 copies/ml showed key resistance mutations in reverse transcriptase. Fourteen had M184V [10 with one to four additional nucleoside analogue mutations (NAMs)]; one had three NAMs only; and the remaining three had K65R. One participant with M184V had major non-nucleoside reverse transcriptase inhibitor-associated mutations, despite no disclosed treatment with this class. Conclusion: Zidovudine/lamivudine/tenofovir has good virological efficacy in advanced HIV disease. In this population, who were infected with HIV-1 subtypes A, C or D, M184V with or without NAMs was the most common route to resistance, whereas K65R was identified less often.

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Kimmel AD, Losina E, Freedberg KA, Goldie SJ. **Diagnostic tests in HIV management: a review of clinical and laboratory strategies to monitor HIV-infected individuals in developing countries.** Bulletin of the World Health Organization 2006;84(7):581-588.

Abstr. We conducted a systematic review on the performance of diagnostic tests for clinical and laboratory monitoring of HIV-infected adults in developing countries. Diagnostic test information collected from computerized databases, bibliographies and the Internet were categorized as clinical (non-laboratory patient information), immunologic (information from immunologic laboratory tests), or virologic (information from virologic laboratory tests). Of the 51 studies selected for the review 28 assessed immunologic tests, 12 virologic tests and seven clinical and immunologic tests. Methods of performance evaluation were primarily sensitivity and specificity for the clinical category and correlation coefficients for immunologic and virologic categories. In the clinical category, the majority of test performance measures was reported as > 70% sensitive and > 65% specific. In the immunologic category, correlation coefficients ranged from $r = 0.54$ to $r = 0.99$ for different CD4 count enumeration techniques, while correlation for CD4 and total lymphocyte counts was between $r = 0.23$ and $r = 0.74$. In the virologic category, correlation coefficients for different human immunodeficiency virus (HIV) ribonucleic acid (RNA) quantification techniques ranged from $r = 0.54$ to $r = 0.90$. Future research requires consensus on designing studies, and collecting and reporting data useful for decision-makers. We recommend classifying information into clinically relevant categories, using a consistent definition of disease across studies and providing measures of both association and accuracy.

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Koulinska IN, Villamor E, Msamanga G, Fawzi W, Blackard J, Renjifo B, Essex M. **Risk of HIV-1 transmission by breastfeeding among mothers infected with recombinant and non-recombinant HIV-1 genotypes.** Virus Research 2006;120(1-2):191-198.

Abstr. Background: Viral genotype and intersubtype recombination may influence the rate and/or timing of mother-to-child HIV-1 transmission. Methods: We determined the HIV-1 subtype of the C2-C5 env and 5'LTR regions from milk and blood samples of 61 Tanzanian mothers who transmitted the virus through breastfeeding and their HIV-1 positive non-transmitting controls. Cases and controls were matched on infant's age at sample collection. All mothers resided in Dar es Salaam, Tanzania. Results: Most infections among cases were due to recombinant viruses (41.0%), followed by HIV-1 subtype A (26.2%), subtype D (19.7%), and subtype C (13.1%). In multivariate analysis including maternal CD4+ cell counts, HIV disease stage, and proviral load in breast milk, the odds of breast milk transmission were 7.2 times higher if the mother carried an intersubtype recombinant genome in comparison to a subtype C virus ($p = 0.02$). Viruses with recombinant LTRs were 4.9 times more likely to be transmitted through breastfeeding than viruses with non-recombinant LTRs of subtype A, C or D combined ($p = 0.01$). Conclusions: This suggested that intersubtype recombinant genomes, and especially recombination within the LTR, might render HIV-1 more fit for transmission via breast milk in comparison with non-recombinant subtypes A, C, and D.

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Labbok MH, Wardlaw T, Blanc A, Clark D, Terreri N. **Trends in exclusive breastfeeding: Findings from the 1990s.** Journal of Human Lactation 2006;22(3):272-276.

Abstr. This article presents trends and differentials in exclusive breastfeeding patterns that occurred in developing settings during the 1990s and considers these trends in relation to the breastfeeding-support activities in that decade. Between 1990 and 2000, the data suggest that exclusive breastfeeding levels in the developing world increased 15% overall among infants younger than 4 months (from 46% to 53%) and among infants older than 6 months (from 34% to 39%). The increase in urban areas is of special note. Urban areas are presumed to be most susceptible to the ambient health system and social and commercial pressures against breastfeeding; the support activities of the 1990s (eg, the Baby-friendly Hospital Initiative and the International Code of Marketing of Breastmilk Substitutes) were developed to address these pressures. Given this, implementation of the Global Strategy for Infant and Young Child Feeding, which supports these proven interventions, should be effective in further increasing optimal breastfeeding practices.

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Lama JR, Sanchez J, Suarez L, Caballero P, Laguna A, Sanchez JL, Whittington WLH, Celum C, Grant RM. **Linking HIV and antiretroviral drug resistance surveillance in Peru: A model for a third-generation HIV sentinel surveillance.** Journal of Acquired Immune Deficiency Syndromes 2006;42(4):501-505.

Abstr. Background: HIV drug resistance surveillance is limited by recruitment and selection bias and by limited information regarding HIV incidence rates, secondary resistance, and treatment prevalence. Methods: A second-generation HIV sentinel surveillance among men who have sex with men (MSM), regardless of prior history of

HIV screening, serostatus, or treatment, was conducted in Peru in 2002. Recent HIV infection was estimated using sensitive/less sensitive enzyme immunoassay testing. Genotypic resistance testing was performed. Results: HIV prevalence was 13.9% (456 HIV positive of 3280 participants). HIV incidence was estimated to be 5.1 per 100 person-years (95% confidence interval: 3.1-8.3). Among 143 MSM who were aware of their HIV infection before testing, only 20 (14.0%) were receiving antiretrovirals (ARV). Mutations conferring ARV resistance were found in 12 (3.3%) of 359 treatment-naïve and 5 (31.3%) of 16 treatment-experienced participants with successful genotyping. One recently infected man from Lima demonstrated 3-class multidrug resistance. The most frequently observed mutations in treatment-naïve, chronically infected persons from Lima were M184V (1.7%), D30N (1.3%), L90M (1.3%), and L10I (1.3%). Conclusions: The prevalence of ARV resistance among treatment-naïve MSM in Peru is low, reflecting limited access to treatment before 2004, and contrasts with the history of ARV treatment in developed countries, where high levels of nucleoside reverse transcriptase inhibitor resistance occurred before introduction of highly active antiretroviral therapy. Linking ARV resistance and HIV sentinel surveillance in developing settings is feasible and should be considered in third-generation HIV sentinel surveillance programs.

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Manosuthi W, Thongyen S, Chumpathat N, Muangchana K, Sungkanuparph S. **Incidence and risk factors of rash associated with efavirenz in HIV-infected patients with preceding nevirapine-associated rash.** HIV Medicine 2006;7(6):378-382.

Abstr. Objective To determine the incidence and risk factors of rash associated with efavirenz in HIV-infected patients with preceding nevirapine-associated rash. Methods A retrospective cohort study was conducted in HIV-infected patients diagnosed with nevirapine-associated rash who subsequently received efavirenz between July 2003 and January 2005. Patients were followed up for 3 months after receiving efavirenz. Possible risk factors, including demographics, previous opportunistic infections, CD4 cell count, viral load, severity of nevirapine-associated rash and concurrent drugs, were studied and compared between those who had (group A) and did not have (group B) rash associated with efavirenz. Results A total of 122 patients (52.5% male) were included in the study, with a mean age of 38.2 years. Median (and interquartile range) CD4 cell count and viral load were 55 (20-167) cells/ μ L and 86 150 (35 321-700 750) HIV-1 RNA copies/mL, respectively. Of the 122 patients, 10 (8.2%) developed rash associated with efavirenz and all required discontinuation of efavirenz. The baseline characteristics of group A (10 patients) and group B (112 patients) were similar. Median (and interquartile range) time from nevirapine discontinuation to efavirenz initiation was 12 (9-21) days in group A and 11 (7-21) days in group B ($P=0.765$). None of the risk factors investigated was associated with developing rash associated with efavirenz. The preceding development of severe nevirapine-associated rash had a trend towards a higher rate in group A than in group B (20.0% vs 10.7%; odds ratio=2.08; 95% confidence interval 0.39-10.97; $P=0.322$). Conclusions The majority (> 90%) of HIV-infected patients with CD4 counts < 200 cells/ μ L who had preceding nevirapine-associated rash could tolerate efavirenz well. Efavirenz may be an option for subsequent use in these patients, particularly in those who had preceding nevirapine-associated rash.

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May MT, Sterne JAC, Costagliola D, Sabin CA, Phillips AN, Justice AC, Dabis F, Gill J, Lundgren J, Hogg RS, de Wolf F, Fatkenheuer G, Staszewski S, Monforte AD, Egger M, Sterne J, Weller I, May M, Beckthold B, Yip B, Dauer B, Fusco J, Lanoy E, Rickenbach M, Lavignolle V, Sighem A, Pereira E, Pezzotti P, Phillips A, Sabin C, Schmeisser N. **HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: a collaborative analysis.** Lancet 2006;368(9534):451-458.

Abstr. Background Highly active antiretroviral therapy (HAART) for the treatment of HIV infection was introduced a decade ago. We aimed to examine trends in the characteristics of patients starting HAART in Europe and North America, and their treatment response and short-term prognosis. Methods We analysed data from 22 217 treatment-naïve HIV-1-infected adults who had started HAART and were followed up in one of 12 cohort studies. The probability of reaching 500 or less HIV-1 RNA copies per mL by 6 months, and the change in CD4 cell counts, were analysed for patients starting HAART in 1995-96, 1997, 1998, 1999, 2000, 2001, and 2002-03. The primary endpoints were the hazard ratios for AIDS and for death from all causes in the first year of HAART which were estimated using Cox regression.

Results The proportion of heterosexually infected patients increased from 20% in 1995-96 to 47% in 2002-03, and the proportion of women from 16% to 32%. The median CD4 cell count when starting HAART increased from 170 cells per μ L in 1995-96 to 269 cells per μ L in 1998 but then decreased to around 200 cells per μ L. In 1995-96, 58% achieved HIV-1 RNA of 500 copies per mL or less by 6 months compared with 83% in 2002-03. Compared with 1998, adjusted hazard ratios for AIDS were 1.07 (95% CI 0.84-1.36) in 1995-96 and

1.35 (1.06-1.71) in 2002-03. Corresponding figures for death were 0.87 (0.56-1.36) and 0.96 (0.61-1.51). Interpretation Virological response after starting HAART improved over calendar years, but such improvement has not translated into a decrease in mortality.

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Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, Rachlis B, Wu P, Cooper C, Thabane L, Wilson K, Guyatt GH, Bangsberg DR. **Adherence to antiretroviral therapy in sub-Saharan Africa and North America - A meta-analysis.** JAMA 2006;296(6):679-690.

Abstr. Context Adherence to antiretroviral therapy is a powerful predictor of survival for individuals living with human immunodeficiency virus (HIV) and AIDS. Concerns about incomplete adherence among patients living in poverty have been an important consideration in expanding the access to antiretroviral therapy in sub-Saharan Africa. Objective To evaluate estimates of antiretroviral therapy adherence in sub-Saharan Africa and North America. Data Sources Eleven electronic databases were searched along with major conference abstract databases (inclusion dates: inception of database up until April 18, 2006) for all English-language articles and abstracts; and researchers and treatment advocacy groups were contacted. Study Selection and Data Abstraction To best reflect the general population, studies of mixed populations in both North America and Africa were selected. Studies evaluating specific populations such as men only, homeless individuals, or drug users, were excluded. The data were abstracted in duplicate on study adherence outcomes, thresholds used to determine adherence, and characteristics of the populations. A random-effects meta-analysis was performed in which heterogeneity was examined using multivariable random-effects logistic regression. A sensitivity analysis was performed using Bayesian methods. Data Synthesis Thirty-one studies from North America (28 full-text articles and 3 abstracts) and 27 studies (9 full-text articles and 18 abstracts) from sub-Saharan Africa were included. African studies represented 12 sub-Saharan countries. Of the North American studies, 71% used patient self-report to assess adherence; this was true of 66% of the African assessments. Studies reported similar thresholds for adherence monitoring (eg, 100%, > 95%, > 90%, > 80%). A pooled analysis of the North American studies (17 573 patients total) indicated a pooled estimate of 55% (95% confidence interval, 49%-62%; I-2, 98.6%) of the populations achieving adequate levels of adherence. Our pooled analysis of African studies (12 116 patients total) indicated a pooled estimate of 77% (95% confidence interval, 68%-85%; I-2, 98.4%). Study continent, adherence thresholds, and study quality were significant predictors of heterogeneity. Bayesian analysis was used as an alternative statistical method for combining adherence rates and provided similar findings. Conclusion Our findings indicate that favorable levels of adherence, much of which was assessed via patient self-report, can be achieved in sub-Saharan African settings and that adherence remains a concern in North America.

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Moore DM, Hogg RS, Yip B, Craib K, Wood E, Montaner JSG. **CD4 percentage is an independent predictor of survival in patients starting antiretroviral therapy with absolute CD4 cell counts between 200 and 350 cells/mu L.** HIV Medicine 2006;7(6):383-388.

Abstr. Objective To determine the prognostic value of baseline CD4 percentage in terms of patient survival in comparison to absolute CD4 cell counts for HIV-positive patients initiating highly active antiretroviral therapy (HAART). Methods A population-based cohort study of 1623 antiretroviral therapy-naive HIV-positive individuals who initiated HAART between 1 August 1996 and 30 June 2002 was conducted. Cumulative mortality rates were estimated using Kaplan-Meier methods. Cox proportional hazards regression was used to model the effect of baseline CD4 strata and CD4 percentage strata and other prognostic variables on survival. A subgroup analysis was conducted on 417 AIDS-free subjects with baseline CD4 counts between 200 and 350 cells/mu L. Results In multivariate models, low CD4 percentages were associated with increased risk of death [CD4% < 5, relative hazard (RH)=4.46; CD4% 5-14, RH=2.43; P < 0.01 for both] when compared with those subjects with an initial CD4 fraction of 15% or greater, but had less predictive value than absolute CD4 counts. In subgroup analyses where absolute CD4 strata were not associated with mortality, a baseline CD4 fraction below 15% [RH=2.71; 95% confidence interval (CI) 1.20-6.10], poor adherence to therapy and baseline viral load > 100 000 HIV-1 RNA copies/mL were associated with an increased risk of death. Conclusion CD4 percentages below 15% are independent predictors of mortality in AIDS-free patients starting HAART, including those with CD4 counts between 200 and 350 cells/mu L. CD4 percentage should be considered for inclusion in guidelines used to determine when to start therapy.

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Sacktor N, Nakasujja N, Skolasky R, Robertson K, Wong M, Musisi S, Ronald A, Katabira E. **Antiretroviral therapy improves cognitive impairment in HIV plus individuals in sub-Saharan Africa.** *Neurology* 2006;67(2):311-314.

Abstr. Background: Highly active antiretroviral therapy (HAART) can improve cognitive performance in some patients with HIV-associated cognitive impairment in the United States. The effect of HAART on HIV dementia in sub-Saharan Africa is largely unknown. Objective: To evaluate neuropsychological test and functional performance in HIV+ individuals after 3 and 6 months of HAART in Uganda. Methods: Twenty-three HIV individuals receiving HAART also received a detailed clinical history, neuropsychological testing, and a functional assessment. Follow-up evaluations were performed at 3 and 6 months after baseline. Longitudinal changes in the HIV dementia stage, the mean Z score for each neuropsychological test, and the Karnofsky Functional Performance Scale were evaluated at 3 and 6 months. Results: The mean (SD) CD4 cell count improved from 71 (15) at baseline to 161 (30) at 3 months ($p = 0.005$) and 222 (46) at 6 months ($p < 0.001$). Improvements were found in the Memorial Sloan Kettering HIV dementia stage and in tests of verbal memory, psychomotor speed, and executive functioning after 3 and 6 months of HAART ($p < 0.001$ at 6 months for each neuropsychological test). There was also improvement in the Karnofsky Functional Performance Scale at both 3 and 6 months after the initiation of HAART ($p < 0.001$). Conclusion: Highly active antiretroviral therapy (HAART) can be associated with improvement in neurocognitive and functional performance in HIV+ individuals in sub-Saharan Africa. These results suggest that HAART, if available in areas with limited resources in sub-Saharan Africa, should be provided for patients with HIV-associated cognitive impairment.

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Safren SA, Kumarasamy N, Hosseinipour M, Harwood MM, Hoffman I, McCauley M, Jumbe A, Nyirenda C, Mimiaga MJ, Solomon S, Celentano D, Mayer KH. **Perceptions about the acceptability of assessments of HIV medication adherence in Lilongwe, Malawi and Chennai, India** *AIDS and Behavior* 2006;10(4):443-450.

Abstr. Little research exists on acceptability issues related to assessments of adherence to ART in resource-poor settings. To help prepare for two large-scale, multisite ART intervention trials, this qualitative study of individuals in Chennai, India (49 men, 11 women; 33 taking ART, 27 not) and Lilongwe, Malawi (5 men, 5 women, all taking ART) examined potential limitations of different types of adherence assessments: an adherence questionnaire, a pill diary, a pillbox, an electronic pill cap, and a medication punch card. Many participants reported that the various assessments would be acceptable. Potential limitations included issues surrounding literacy, the desire to appease one's medical provider, privacy and stigma, and "cheating." These potential limitations are similar to the limitations of these assessments in Western settings. However, the data highlight the need to consider individual patient level concerns when assessing ART adherence in different cultural settings. Innovative ways of monitoring adherence while maintaining standardization across sites are required in multisite trials.

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Abstr. Background: Single-dose nevirapine given to women and infants reduces mother-to-child HIV transmission, but nevirapine resistance develops in a large percentage of women. Objective: To determine whether the maternal nevirapine dose could be eliminated in the setting of zidovudine prophylaxis. Design, setting, and participants: A 2 x 2 factorial, randomized, clinical trial, with a double-blinded peripartum factor designed to assess the equivalence of maternal single-dose nevirapine versus placebo with respect to HIV transmission. A total of 709 HIV-infected pregnant women were randomized from four district hospitals in Botswana, resulting in 694 live first-born infants. HAART was available for women with AIDS. Intervention: All women received a background of zidovudine from 34 weeks' gestation through delivery, and all infants received single-dose nevirapine at birth and zidovudine from birth through 1 month. Women were randomized to receive either single-dose nevirapine or placebo during labor. Main outcome measures: The primary endpoint was infant HIV infection by the 1-month visit. Results: Of the 694 infants in this equivalence study, 15 (4.3%) of 345 in the maternal nevirapine arm were HIV infected by 1 month, versus 13 (3.7%) of 349 in the maternal placebo arm (95% confidence interval for difference, -2.4% to 3.8%), meeting pre-determined equivalence criteria. Nevirapine resistance at 1 month postpartum was detected in 45% of a random sample of women who received nevirapine. Conclusions: In the setting of maternal zidovudine and infant zidovudine plus single-dose

nevirapine, infant HIV infection rates were similar whether women received single-dose nevirapine or placebo. This strategy avoids the potential for maternal nevirapine resistance.

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Abstr. Context The Zambian Ministry of Health has scaled-up human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) care and treatment services at primary care clinics in Lusaka, using predominately nonphysician clinicians. Objective To report on the feasibility and early outcomes of the program. Design, Setting, and Patients Open cohort evaluation of antiretroviral-naïve adults treated at 18 primary care facilities between April 26, 2004, and November 5, 2005. Data were entered in real time into an electronic patient tracking system. Intervention Those meeting criteria for antiretroviral therapy (ART) received drugs according to Zambian national guidelines. Main Outcome Measures Survival, regimen failure rates, and CD4 cell response. Results We enrolled 21 755 adults into HIV care, and 16 198 (75%) started ART. Among those starting ART, 9864 (61%) were women. Of 15 866 patients with documented World Health Organization (WHO) staging, 11 573 (73%) were stage III or IV, and the mean (SD) entry CD4 cell count among the 15 336 patients with a baseline result was 143/ μ L (123/ μ L). Of 1142 patients receiving ART who died, 1120 had a reliable date of death. Of these patients, 792 (71%) died within 90 days of starting therapy (early mortality rate: 26 per 100 patient-years), and 328 (29%) died after 90 days (post-90-day mortality rate: 5.0 per 100 patient-years). In multivariable analysis, mortality was strongly associated with CD4 cell count between 50/ μ L and 199/ μ L (adjusted hazard ratio [AHR], 1.4; 95% confidence interval [CI], 1.0-2.0), CD4 cell count less than 50/ μ L (AHR, 2.2; 95% CI, 1.5-3.1), WHO stage III disease (AHR, 1.8; 95% CI, 1.3-2.4), WHO stage IV disease (AHR, 2.9; 95% CI, 2.0-4.3), low body mass index (<16; AHR, 2.4; 95% CI, 1.8-3.2), severe anemia (<8.0 g/dL; AHR, 3.1; 95% CI, 2.3-4.0), and poor adherence to therapy (AHR, 2.9; 95% CI, 2.2-3.9). Of 11 714 patients at risk, 861 failed therapy by clinical criteria (rate, 13 per 100 patient-years). The mean (SD) CD4 cell count increase was 175/ μ L (174/ μ L) in 1361 of 1519 patients (90%) receiving treatment long enough to have a 12-month repeat. Conclusion Massive scale-up of HIV and AIDS treatment services with good clinical outcomes is feasible in primary care settings in sub-Saharan Africa. Most mortality occurs early, suggesting that earlier diagnosis and treatment may improve outcomes.

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Abstr. Context Postnatal transmission of human immunodeficiency virus-1 (HIV) via breast-feeding reverses gains achieved by perinatal antiretroviral interventions. Objective To compare the efficacy and safety of 2 infant feeding strategies for the prevention of postnatal mother-to-child HIV transmission. Design, Setting, and Patients A 2 x 2 factorial randomized clinical trial with peripartum (single-dose nevirapine vs placebo) and postpartum infant feeding (formula vs breastfeeding with infant zidovudine prophylaxis) interventions. In Botswana between March 27, 2001, and October 29, 2003, 1200 HIV-positive pregnant women were randomized from 4 district hospitals. Infants were evaluated at birth, monthly until age 7 months, at age 9 months, then every third month through age 18 months. Intervention All of the mothers received zidovudine 300 mg orally twice daily from 34 weeks' gestation and during labor. Mothers and infants were randomized to receive single-dose nevirapine or placebo. Infants were randomized to 6 months of breastfeeding plus prophylactic infant zidovudine (breastfed plus zidovudine), or formula feeding plus 1 month of infant zidovudine (formula fed). Main Outcome Measures Primary efficacy (HIV infection by age 7 months and HIV-free survival by age 18 months) and safety (occurrence of infant adverse events by 7 months of age) end points were evaluated in 1179 infants. Results The 7-month HIV infection rates were 5.6% (32 infants in the formula-fed group) vs 9.0% (51 infants in the breastfed plus zidovudine group) (P=.04; 95% confidence interval for difference, -6.4% to -0.4%). Cumulative mortality or HIV infection rates at 18 months were 80 infants (13.9%, formula fed) vs 86 infants (15.1% breastfed plus zidovudine) (P=.60; 95% confidence interval for difference, -5.3% to 2.9%). Cumulative infant mortality at 7 months was significantly higher for the formula-fed group than for the breastfed plus zidovudine group (9.3% vs 4.9%; P=.003), but this difference diminished beyond month 7 such that the time-to-mortality distributions through age 18 months were not significantly different (P=.21). Conclusions Breastfeeding with zidovudine prophylaxis was not as effective as formula feeding in preventing postnatal HIV transmission, but

was associated with a lower mortality rate at 7 months. Both strategies had comparable HIV-free survival at 18 months. These results demonstrate the risk of formula feeding to infants in sub-Saharan Africa, and the need for studies of alternative strategies.

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Toure S, Gabillard D, Inwoley A, Seyler C, Gourvellec G, Anglaret X. **Incidence of neutropenia in HIV-infected African adults receiving co-trimoxazole prophylaxis: a 6-year cohort study in Abidjan, Cote d'Ivoire.** Transactions of the Royal Society of Tropical Medicine and Hygiene 2006;100(8):785-790.

Abstr. In a placebo-controlled trial of co-trimoxazole prophylaxis in Cote d'Ivoire, neutropenia was the most frequent short-term side effect. The long-term incidence of neutropenia in sub-Saharan African adults receiving co-trimoxazole has never been reported. We followed a prospective cohort of HIV-infected adults receiving co-trimoxazole (sulphamethoxazole 800 mg/trimethoprim 160 mg daily) in Abidjan. Grades of neutropenia were successively defined as at least one absolute neutrophil count (ANC) of: <1500/mm³ (severity grade \geq 1), <1000/mm³ (grade \geq 2), <750/mm³ (grade \geq 3) or <500/mm³ (grade 4). In total, 533 adults were followed-up during 1450 person-years, with a total of 3154 ANCs. The probability of remaining free of neutropenia at 48 months was 0.29 (95% CI 0.23-0.34) for grade \geq 1, 0.64 (95% CI 0.60-0.71) for grade \geq 2, 0.82 (95% CI 0.77-0.86) for grade \geq 3 and 0.96 (95% CI 0.93-0.99) for grade 4. The only factor significantly associated with a higher rate of all grades of neutropenia was a low baseline CD4 count. There was no association between any grade of neutropenia and the global risk of serious morbidity during the study period. In adults receiving co-trimoxazole in Abidjan, mild neutropenia is a common observation with no evidence of negative clinical consequences. The consequences of associating co-trimoxazole with other haematotoxic drugs should be carefully assessed.

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Van der Borgh S, de Wit TFR, Janssens V, van der Loeff MFS, Rijckborst H, Lange JMA. **HAART for the HIV-infected employees of large companies in Africa [Viewpoint].** Lancet 2006;368(9534):547-550.

Introduction. The International AIDS Conference held in Durban in 2000 was a watershed for highly active antiretroviral treatment (HAART) in Africa. Since then, HAART in sub-Saharan Africa has been firmly on the international agenda, and access to treatment in resource-poor settings has become a top priority. Multiple initiatives were developed to realise the goal of expanding treatment access (The Global Fund to Fight AIDS, Tuberculosis and Malaria, the US President's Emergency Plan for AIDS Relief, the World Bank's Multi-country AIDS Programme, and many others). Although private sector employers in Africa were some of the first to embark on HAART for their workers (eg, Anglo-American, Compagnie Ivoirienne d'Electricité, Volkswagen South Africa), public sector approaches have now largely surpassed these efforts. Few large companies in Africa have launched comprehensive AIDS treatment schemes for their workers and dependants. Most employers in Africa hesitate to take responsibility, and refer employees to government HIV programmes that are benefiting from international financial support but struggling with implementation. There is an encouraging trend among companies in countries with high prevalence to have HIV policies, but even in countries with prevalences between 5% and 20%, less than half of companies claim to have an HIV policy. In sub-Saharan Africa, only 26% of the companies that have HIV policies provide antiretroviral treatment to their workers. In 2001, Heineken decided to add HAART to the package of medical benefits for employees. Where the existing medical policy extended to spouses and family members, dependants would also benefit from HAART. The programme was implemented in collaboration with PharmAccess Foundation, a non-government organisation from the Netherlands dedicated to sustainable quality AIDS treatment in resource-poor settings. In many business meetings, Heineken was asked what justified the decision to offer treatment to their employees, but on those occasions the question was reversed and other companies asked why they did not offer HAART to employees. Various reasons were given; here we point out why such justifications are not valid.

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Yeni P, Cooper DA, Aboulker JP, Babiker AG, Carey D, Darbyshire JH, et al. **Virological and immunological outcomes at 3 years after starting antiretroviral therapy with regimens containing non-nucleoside reverse transcriptase inhibitor, protease inhibitor, or both in INITIO: open-label randomised trial.** Lancet 2006;368(9532):287-298.

Abstr. Background Antiretroviral therapy has greatly reduced HIV mortality and morbidity. However, the best sequence of regimens and implications of initial regimen for long-term therapeutic success are not well defined. Methods In INITIO, a large international randomised trial, we compared antiretroviral therapy with two nucleoside analogue reverse transcriptase inhibitors (didanosine+stavudine) plus either a non-nucleoside reverse

transcriptase inhibitor (efavirenz, EFV) or a protease inhibitor (nelfinavir, NFV), or both (EFV/NFV), in patients with HIV-1 infection who had not previously received antiretroviral drugs. Primary outcomes were proportion with undetectable HIV RNA in plasma, and change in CD4 count from baseline at 3 years. Analyses were by intention-to-treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN44582462. Findings We followed up 911 participants (297 EFV, 311 NFV, 303 EFV/NFV). At 3 years, the proportion with HIV RNA less than 50 copies per mL was highest in the EFV group (188 [74%] EFV, 162 [62%] NFV, 155 [62%] EFV/NFV, $p=0.004$). Mean (95% CI) increases in CD4 count were 316×10^6 cells per L (288-343) for EFV, 289×10^6 cells per L (262-316) for NFV, and 274×10^6 cells per L (231-291) for EFV/NFV ($p=0.1$). Fewer participants in the EFV group than in the other groups stopped adequate antiretroviral therapy for more than 30 days ($p=0.005$). Participants in the EFV/NFV group had shorter time to stopping the initial regimen ($p<0.0001$) and to a treatment modifying adverse event ($p=0.04$) than those in the other groups. Interpretation Starting antiretroviral therapy with a three-drug/two-class regimen including efavirenz was better than starting with regimens including nelfinavir or efavirenz plus nelfinavir in terms of virological suppression and durability of the initial regimen. The shorter time on adequate antiretroviral therapy or to a treatment-modifying adverse event might explain the absence of additional benefit for the four-drug regimen.

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