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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

Au JT, Kayitenkore K, Shutes E, Karita E, Peters PJ, Tichacek A, Allen SA. **Access to adequate nutrition is a major potential obstacle to antiretroviral adherence among HIV-infected individuals in Rwanda.** *AIDS* 2006;20(16):2116-2118.

Abstr. Despite the massive expansion of antiretroviral drugs in Africa, little is known about the resulting changes in sexual behavior or obstacles to antiretroviral therapy (ART) adherence. Our evaluation of Rwandan adults on ART found no increase in risky sexual behaviors, but an obstacle to ART initiation and adherence for 76% of patients was a fear of developing too much appetite without enough to eat. Access to adequate nutrition may be a major determinant for long-term adherence to ART.

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Fiscus SA, Cheng B, Crowe SM, Demeter L, Jennings C, Miller V, Respass R, Stevens W. **HIV-1 viral load assays for resource-limited settings - art. no. e417.** *Plos Medicine* 2006;3(10):1743-1750.

Introduction. Tremendous strides have been made in treating HIV-1 infection in industrialized countries. Combination therapy with antiretroviral (ARV) drugs suppresses virus replication, delays disease progression, and reduces mortality. In industrialized settings, plasma viral load assays are used in combination with CD4 cell counts to determine when to initiate therapy and when a regimen is failing. In addition, unlike serologic assays, these assays may be used to diagnose perinatal or acute HIV-1 infection. Unfortunately, the full benefits of antiretroviral drugs and monitoring tests have not yet reached the majority of HIV-1-infected patients who live in countries with limited resources. In this article we discuss existing data on the performance of alternative viral load assays that might be useful in resource-limited settings. Our search strategy and selection criteria for relevant studies are shown.

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<http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371%2Fjournal.pmed.0030417>

Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, Zeller K, Andrews J, Friedland G. **Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa.** *Lancet* 2006;368(9547):1575-1580.

Abstr. Background The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in co-infected patients have improved with antiretroviral therapy, but drug-resistant tuberculosis has emerged as a major cause of death. We assessed the prevalence and consequences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in a rural area in KwaZulu Natal, South Africa. Methods We undertook enhanced surveillance for drug-resistant tuberculosis with sputum culture and drug susceptibility testing in patients with known or suspected tuberculosis. Genotyping was done for isolates resistant to first-line and second-line drugs. Results From January, 2005, to March, 2006, sputum was obtained from 1539 patients. We detected MDR tuberculosis in 221 patients, of whom 53 had XDR tuberculosis. Prevalence among 475 patients with culture-confirmed tuberculosis was 39% (185 patients) for MDR and 6% (30) for XDR tuberculosis. Only 55% (26 of 47) of patients with XDR tuberculosis had never been previously treated for tuberculosis; 67% (28 of 42) had a recent hospital admission. All 44 patients with XDR tuberculosis who were tested for HIV were co-infected. 52 of 53 patients with XDR tuberculosis died, with median survival of 16 days from time of diagnosis (IQR 6-37) among the 42 patients with confirmed dates of death. Genotyping of isolates showed that 39 of 46 (85%, 95% CI 74-95) patients with XDR tuberculosis had similar strains. Conclusions MDR tuberculosis is more prevalent than previously realised in this setting. XDR tuberculosis has been transmitted to HIV co-infected patients and is associated with high mortality. These observations warrant urgent intervention and threaten the success of treatment programmes for tuberculosis and HIV.

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Hewitt K, Steketee R, Mwapasa V, Whitworth J, French N. **Interactions between HIV and malaria in non-pregnant adults: evidence and implications.** *AIDS* 2006;20(16):1993-2004.

Introduction. Malaria and HIV are two of the most common and important health problems facing developing countries. It is estimated that over 40 million people are living with HIV globally and there are 350–500 million clinical malaria episodes annually. Even modest interactions between the two infections would have substantial public health implications in resource-constrained countries, especially in sub-Saharan Africa, where both infections are highly prevalent. Our current immunological knowledge suggests potential for a detrimental interaction in both directions. HIV infection impairs T-cell immunity, which is of crucial importance for antimalarial responses. Therefore, in theory, HIV immunosuppression should increase the risk and severity of

malarial infection. In addition, malaria infection activates T-cells, promoting HIV replication. Since increased HIV RNA levels are associated with accelerated disease progression, malaria could potentially facilitate faster progression to AIDS and death.

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Hogg RS, Bangsberg DR, Lima VD, Alexander C, Bonner S, Yip B, Wood E, Dong WWY, Montaner JSG, Harrigan PR. **Emergence of drug resistance is associated with an increased risk of death among patients first starting HAART - art. no. e356.** Plos Medicine 2006;3(9):1570-1578.

Abstr. Background The impact of the emergence of drug-resistance mutations on mortality is not well characterized in antiretroviral-naive patients first starting highly active antiretroviral therapy (HAART). Patients may be able to sustain immunologic function with resistant virus, and there is limited evidence that reduced sensitivity to antiretrovirals leads to rapid disease progression or death. We undertook the present analysis to characterize the determinants of mortality in a prospective cohort study with a median of nearly 5 y of follow-up. The objective of this study was to determine the impact of the emergence of drug-resistance mutations on survival among persons initiating HAART. Methods and Findings Participants were antiretroviral therapy naive at entry and initiated triple combination antiretroviral therapy between August 1, 1996, and September 30, 1999. Marginal structural modeling was used to address potential confounding between time-dependent variables in the Cox proportional hazard regression models. In this analysis resistance to any class of drug was considered as a binary time-dependent exposure to the risk of death, controlling for the effect of other time-dependent confounders. We also considered each separate class of mutation as a binary time-dependent exposure, while controlling for the presence/absence of other mutations. A total of 207 deaths were identified among 1,138 participants over the follow-up period, with an all cause mortality rate of 18.2%. Among the 679 patients with HIV-drug-resistance genotyping done before initiating HAART, HIV-drug resistance to any class was observed in 53 (7.8%) of the patients. During follow-up, HIV-drug resistance to any class was observed in 302 (26.5%) participants. Emergence of any resistance was associated with mortality (hazard ratio: 1.75 [95% confidence interval: 1.27, 2.43]). When we considered each class of resistance separately, persons who exhibited resistance to non-nucleoside reverse transcriptase inhibitors had the highest risk: mortality rates were 3.02 times higher (95% confidence interval: 1.99, 4.57) for these patients than for those who did not exhibit this type of resistance. Conclusions We demonstrated that emergence of resistance to non-nucleoside reverse transcriptase inhibitors was associated with a greater risk of subsequent death than was emergence of protease inhibitor resistance. Future research is needed to identify the particular subpopulations of men and women at greatest risk and to elucidate the impact of resistance over a longer follow-up period.

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Moyle GJ, Sabin CA, Cartledge J, Johnson M, Wilkins E, Churchill D, Hay P, Fakoya A, Murphy M, Scullard G, Leen C, Reilly G. **A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipoatrophy.** AIDS 2006;20(16):2043-2050.

Abstr. Background: Long-term antiretroviral therapy, while dramatically reducing HIV-related morbidity and mortality, is associated with metabolic and morphological changes. Peripheral fat loss, lipoatrophy, appears most associated with prolonged therapy with thymidine nucleoside analogues. Methods: A randomized, open-label, comparative study of switching from a thymidine nucleoside analogue to either tenofovir disoproxil fumarate (QF) or abacavir in 105 individuals on successful antiretroviral therapy with clinically evident moderate to severe lipoatrophy. Results: Individuals were randomized to tenofovir DF (52) or abacavir (53). The switch was well tolerated and the majority of patients completed 48 weeks of study. One individual in the tenofovir DF group and three in the abacavir group discontinued due to drug-related adverse events. Both groups similarly maintained virological control. Limb fat mass increased similarly in both groups: mean increases by week 48 of 329 and 483 g in tenofovir DF and abacavir groups, respectively [mean 95% confidence interval for difference, -154.3 (range -492.8 to 184.3)]. This change from baseline was statistically significant in both groups (tenofovir DF, P=0.01; abacavir, P=0.0001). Mean total cholesterol, low density lipoprotein cholesterol and triglycerides improved modestly with switching to tenofovir DF but were unchanged with abacavir. The changes in these parameters were significantly greater in the tenofovir DF arm relative to abacavir. Conclusions: Switching from a thymidine nucleoside analogue to either tenofovir DF or abacavir leads to significant improvement in limb fat mass over 48

weeks. Tenofovir DF may have modest advantages over abacavir for changes in lipids. Peripheral lipoatrophy, when clinically apparent, resolves slowly following treatment switching.

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Peters MG, Andersen J, Lynch P, Liu T, Alston Smith B, Brosgart CL, Jacobson JM, Johnson VA, Poflard RB, Rooney JF, Sherman KE, Swindells S, Polsky B. **Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127.** *Hepatology* 2006;44(5):1110-1116.

Abstr. Chronic hepatitis B virus (HBV) infection is an important cause of morbidity and mortality in subjects coinfecting with HIV. Tenofovir disoproxil fumarate (TDF) and adefovir dipivoxil (ADV) are licensed for the treatment of HIV-1 and HBV infection, respectively, but both have in vivo and in vitro activity against HBV. This study evaluated the anti-HBV activity of TDF compared to ADV in HIV/HBV-coinfecting subjects. ACTG A5127 was a prospective randomized, double-blind, placebo-controlled trial of daily 10 mg of ADV versus 300 mg of TDF in subjects with HBV and HIV coinfection on stable ART, with serum HBV DNA \geq 100,000 copies/mL, and plasma HIV-1 RNA \leq 10,000 copies/mL. This study closed early based on results of a prespecified interim review, as the primary noninferiority end point had been met without safety issues. Fifty-two subjects were randomized. At baseline, 73% of subjects had a plasma HIV-1 RNA $<$ 50 copies/mL, 86% were HBeAg positive, 94% were 3TC resistant, median serum ALT was 52 IU/L, and 98% had compensated liver disease. The mean time-weighted average change in serum HBV DNA from baseline to week 48 (DAVG(48)) was -4.44 log₁₀ copies/mL for TDF and -3.21 log₁₀ copies/mL for ADV. There was no difference in toxicity between the 2 treatment arms, with 11 subjects (5 ADV and 6 TDF) experiencing elevations of serum ALT on treatment. In conclusion, over 48 weeks, treatment with either ADV or TDF resulted in clinically important suppression of serum HBV DNA. Both drugs are safe and efficacious for patients coinfecting with HBV and HIV.

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Rexroad VE, Parsons TL, Hamzeh FM, Li XB, Dreyfuss ML, Stamper PD, Gray RH. **Stability of nevirapine suspension in prefilled oral syringes used for reduction of mother-to-child HIV transmission.** *Journal of Acquired Immune Deficiency Syndromes* 2006;43(3):373-375.

Abstr. Objective: To reduce mother-to-child transmission (MTCT) of HIV, we assessed the stability of nevirapine suspension in an oral dosing syringe over a range of storage conditions. Design: A mother-to-child transmission dosing kit, containing a maternal nevirapine tablet and infant nevirapine suspension in an oral syringe that can be dispensed to the pregnant woman to use at delivery. However, the manufacturer only packages nevirapine in 240 mL, multidose containers and there are no published stability data for nevirapine suspension repackaged in an oral syringe. Methods: Nevirapine suspension 6 mg/0.6 mL in 3 mL amber BAXA Exacta-Med Oral Dispensers (Baxa Corporation, Englewood, CO) were stored under the following conditions: 26 degrees C/high relative humidity (RH), 40 degrees C/low RH, 40 degrees C/high RH, refrigerated and frozen -30 degrees C for 6 months. The samples were assayed monthly for nevirapine by HPLC-UV. At 3, 4, and 6 months the samples were cultured for pathogens. Results: There were no significant decreases in nevirapine concentrations in the prefilled syringes compared with baseline. Nevirapine became more concentrated in syringes incubated at 40°C/low RH due to evaporation resulting in the suspension becoming more viscous. No pathogens were cultured. Conclusions: Nevirapine suspension is stable and pathogen free at varying conditions for 6 months in Baxa Exacta-Med Oral Dispensers.

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Shah SN, Smith EE, Obonyo CO, Kain KC, Bloland PB, Slutsker L, Hamel MJ. **HIV immunosuppression and antimalarial efficacy: Sulfadoxine-pyrimethamine for the treatment of uncomplicated malaria in HIV-infected adults in Siaya, Kenya.** *Journal of Infectious Diseases* 2006;194(11):1519-1528.

Abstr. Background. The altered immune response of persons with human immunodeficiency virus (HIV) infection could result in increased rates of antimalarial treatment failure. We investigated the influence of HIV infection on the response to sulfadoxine-pyrimethamine treatment. Methods. Febrile adults with *Plasmodium falciparum* parasitemia were treated with sulfadoxine-pyrimethamine and were monitored for 28 days. HIV status and CD4 cell count were determined at study enrollment. Results. Of the adults enrolled in the study, 508 attended all follow-up visits, including 130 HIV-uninfected adults, 256 HIV-infected adults with a high CD4 cell count (\geq 200 cells/ μ L), and 122 HIV-infected adults with a low CD4 cell count ($<$ 200 cells/mL). The hazard

of treatment failure at day 28 of follow-up was significantly higher for HIV-infected adults with a low CD4 cell count (20.5%) than for HIV-uninfected adults (7.7%). Anemia (hemoglobin level, < 110 g/L) modified the effect of HIV status on treatment failure. When we controlled for fever and parasite density, the hazard of treatment failure for HIV-infected adults with a low CD4 cell count and anemia was 3.4 times higher than that for HIV-uninfected adults (adjusted hazard ratio, 3.38; 95% confidence interval, 1.56-7.34). Conclusions. HIV-infected persons with a low CD4 cell count and anemia have an increased risk of antimalarial treatment failure. The response to malaria treatment in HIV-infected persons must be carefully monitored. Proven measures for the control and prevention of malaria must be incorporated into the basic package of services provided by HIV/acquired immunodeficiency syndrome care and treatment programs in malarious areas.

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Van Geertruyden JP, Mulenga M, Kasongo W, Polman K, Colebunders R, Kestens L, U DA. **CD4 T-cell count and HIV-1 infection in adults with uncomplicated malaria.** Journal of Acquired Immune Deficiency Syndromes 2006;43(3):363-367.

Abstr. Background: HIV-1 negative children with malaria have reversible lymphocyte and CD4 count decreases. We assessed the impact of malaria parasitemia on the absolute CD4 count in both HIV-1-infected and non-HIV-infected adults. Methods: In Ndola, Zambia, at the health-center level, we treated 327 nonpregnant adults for confirmed, uncomplicated, clinical malaria. We assessed HIV-1 status, CD4 count, and HIV-1 viral load (if HIV-1 infected) at enrollment and at 28 and 45 days after treatment. Results: After successful antimalarial treatment, the median CD4 count at day 28 of follow-up increased from 468 to 811 cells/P.L in HIV-1-negative and from 297 to 447 cells/RL in HIV-1-positive patients (paired t test, $P < 0.001$ for both). CD4 count increment was inversely correlated with CD4 count at day 0 in both HIV-1 negative ($P < 0.001$) and HIV-1-positive patients ($P < 0.03$). After successful treatment, the proportion of patients with CD4 count < 200/ μ L at day 45 decreased from 9.6% to 0% in HIV-1-negative and from 28.7% to 13.2% in HIV-1-positive malaria patients ($P < 0.001$ for both). In patients with detectable but mostly asymptomatic parasitemia, CD4 count and, if HIV-1-infected, viral load at day 45 of follow-up were similar to those observed at enrollment. Conclusion: Interpretation of absolute CD4 count might be biased during or just after a clinical malaria episode. Therefore, in malaria endemic areas, before taking any decision on the management of HIV-1-positive individuals, their malaria status should be assessed.

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Walter J, Mwiya M, Scott N, Kasonde P, Sinkala M, Kankasa C, Kauchali S, Aldrovandi GM, Thea DM, Kuhn L. **Reduction in preterm delivery and neonatal mortality after the introduction of antenatal cotrimoxazole prophylaxis among HIV-infected women with low CD4 cell counts.** Journal of Infectious Diseases 2006;194(11):1510-1518.

Abstr. Background. Cotrimoxazole prophylaxis is recommended for subgroups of human immunodeficiency virus (HIV)-infected adults and children to reduce all-cause morbidity and mortality. We investigated whether antenatal cotrimoxazole prophylaxis begun during pregnancy for HIV-infected pregnant women with low CD4 cell counts would affect birth outcomes. Methods. Cotrimoxazole prophylaxis was introduced as a routine component of antenatal care for HIV-infected women with CD4 cell counts < 200 cells/mL during the course of a trial of mother-to-child HIV transmission in Lusaka, Zambia. Rates of preterm delivery, low birth weight, and neonatal mortality were compared for women with low CD4 cell counts before and after its introduction. Results. Among 255 women with CD4 cell counts < 200 cells/ μ L, the percentage of preterm births (≤ 34 weeks of gestation) was lower (odds ratio [OR], 0.49 [95% confidence interval {CI}, 0.24-0.98]) after cotrimoxazole prophylaxis was introduced than before; there was a significant decrease in neonatal mortality (9% to 0%; $P = .01$) and a trend toward increased birth weight ($\beta = 114$ g [95% CI, -42 to 271 g]). In contrast, there were no significant changes in these parameters over the same time interval among women with CD4 cell counts ≥ 200 cells/ μ L. Conclusion. Antenatal provision of cotrimoxazole for HIV-infected pregnant women with low CD4 cell counts may have indirect benefits for neonatal health.

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Watts DH, Mofenson LM. **Cotrimoxazole prophylaxis in HIV-infected pregnant women: Only a first step [Editorial]**. *Journal of Infectious Diseases* 2006;194(11):1478-1480.

Introduction. In resource-rich countries, during the era before the availability of highly active antiretroviral therapy (HAART), prophylaxis with cotrimoxazole (CTX) was one of the first interventions shown to reduce morbidity and mortality among HIV-infected individuals by reducing the incidence of *Pneumocystis jiroveci* pneumonia. Prophylaxis with CTX is still recommended for persons with CD4 cell counts <200 cells/L, even for those receiving HAART.

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Weidle PJ, Wamai N, Solberg P, Liechty C, Sendagala S, Were W, Mermin J, Buchacz K, Behumbiize P, Ransom RL, Bunnell R. **Adherence to antiretroviral therapy in a home-based AIDS care programme in rural Uganda.** *Lancet* 2006;368(9547):1587-1594.

Abstr. Background Poverty and limited health services in rural Africa present barriers to adherence to antiretroviral therapy that necessitate innovative options other than facility-based methods for delivery and monitoring of such therapy. We assessed adherence to antiretroviral therapy in a cohort of HIV-infected people in a home-based AIDS care programme that provides the therapy and other AIDS care, prevention, and support services in rural Uganda. Methods HIV-infected individuals with advanced HIV disease or a CD4-cell count of less than 250 cells per mu L were eligible for antiretroviral therapy. Adherence interventions included group education, personal adherence plans developed with trained counsellors, a medicine companion, and weekly home delivery of antiretroviral therapy by trained lay field officers. We analysed factors associated with pill count adherence (PCA) of less than 95%, medication possession ratio (MPR) of less than 95%, and HIV viral load of 1000 copies per mL or more at 6 months (second quarter) and 12 months (fourth quarter) of follow-up. Findings 987 adults who had received no previous antiretroviral therapy (median CD4-cell count 124 cells per mu L, median viral load 217 000 copies per mL) were enrolled between July, 2003, and May, 2004. PICA of less than 95% was calculated for 0.7-2.6% of participants in any quarter and MPR of less than 95% for 3.3-11.1%. Viral load was below 1000 copies per mL for 894 (98%) of 913 participants in the second quarter and for 860 (96%) of 894 of participants in the fourth quarter. In separate multivariate models, viral load of at least 1000 copies per mL was associated with both PICA below 95% (second quarter odds ratio 10.6 [95% CI 2.45-45.7]; fourth quarter 14.5 [2.51-83.6]) and MPR less than 95% (second quarter 9.44 [3.40-26.2]; fourth quarter 10.5 [4.22-25.9]). Interpretation Good adherence and response to antiretroviral therapy can be achieved in a home-based AIDS care Programme in a resource-limited rural African setting. Health-care systems must continue to implement, evaluate, and modify interventions to overcome barriers to comprehensive AIDS care programmes, especially the barriers to adherence with antiretroviral therapy.

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