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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

Badri M, D LS, Wood R. **Short-term risk of AIDS or death in people infected with HIV-1 before antiretroviral therapy in South Africa: a longitudinal study.** *Lancet* 2006;368(9543):1254-1259.

Abstr. Background In sub-Saharan Africa, data for short-term risk of AIDS or death, which might inform decisions about when to start antiretroviral therapy (ART), are scarce. Our aim was to investigate these risks in patients who had no access to ART or who were given zidovudine alone. Methods 6-month risks (%) of death, AIDS, and combined risk of AIDS and death (AIDS/death) were calculated according to CD4-cell count category of less than 200 cells per mu L, 200-350 cells per mu L, or greater than 350 cells per mu L, stratified by WHO clinical stages 1 and 2 combined, 3, or 4 in untreated patients (n=1399) seeking care in tertiary public-sector HIV clinics before widespread availability of ART in Cape Town, South Africa. Findings Risk of death for WHO stages 1 and 2 was 3.5% for those with less than 200 cells per mu L, 2.8% for 200-350 cells per mu L, and 1.2% for greater than 350 cells per mu L. The corresponding rates for WHO stage 3 were 10.8%, 4.3%, and 4.9% and for stage 4, 22.2%, 10.3%, and 13.8%. 52% (90) of deaths took place in patients without AIDS. 6-month risk of AIDS for WHO stages 1 and 2 was 3.5% for those with less than 200 cells per mu L, 1.6% for 200-350 cells per mu L, and zero for greater than 350 cells per mu L. The corresponding rates for those with WHO stage 3 disease were 17.4%, 7.0%, and 2.2%. Interpretation In this study, risk of AIDS in patients with a CD4-cell count of less than 200 cells per mu L or greater than 350 cells per mu L was similar to that previously reported from European cohorts, but was 1.9 times greater for those with CD4-cell counts of between 200 and 350 cells per mu L. The high death rate before development of AIDS and a high risk of AIDS in those with CD4-cell counts of 200-350 cells per mu L indicate that delay in initiation of ART is associated with increased morbidity and mortality. These findings might help to amend criteria for start of ART in resource-limited settings.

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Badri M, Maartens G, Mandalia S, Bekker LG, Penrod JR, Platt RW, Wood R, Beck EJ. **Cost-effectiveness of highly active antiretroviral therapy in South Africa.** *PLoS Medicine* 2006;3(1):e4.

Abstr. BACKGROUND: Little information exists on the impact of highly active antiretroviral therapy (HAART) on health-care provision in South Africa despite increasing scale-up of access to HAART and gradual reduction in HAART prices. METHODS AND FINDINGS: Use and cost of services for 265 HIV-infected adults without AIDS (World Health Organization [WHO] stage 1, 2, or 3) and 27 with AIDS (WHO stage 4) receiving HAART between 1995 and 2000 in Cape Town were compared with HIV-infected controls matched for baseline WHO stage, CD4 count, age, and socioeconomic status, who did not receive antiretroviral therapy (ART; No-ART group). Costs of service provision (January 2004 prices, USD 1 = 7.6 Rand) included local unit costs, and two scenarios for HAART prices for WHO recommended first-line regimens: scenario 1 used current South African public-sector ART drug prices of \$730 per patient-year (PPY), whereas scenario 2 was based on the anticipated public-sector price for locally manufactured drug of \$181 PPY. All analyses are presented in terms of patients without AIDS and patients with AIDS. For patients without AIDS, the mean number of inpatient days PPY was 1.08 (95% confidence interval [CI]: 0.97-1.19) for the HAART group versus 3.73 (95% CI: 3.55-3.97) for the No-ART group, and 8.71 (95% CI: 8.40-9.03) versus 4.35 (95% CI: 4.12-5.61), respectively, for mean number of outpatient visits PPY. Average service provision PPY was \$950 for the No-ART group versus \$1,342 and \$793 PPY for the HAART group for scenario 1 and 2, respectively, whereas the incremental cost per life-year gained (LYG) was \$1,622 for scenario 1 and \$675 for scenario 2. For patients with AIDS, mean inpatients days PPY was 2.04 (95% CI: 1.63-2.52) for the HAART versus 15.36 (95% CI: 13.97-16.85) for the No-ART group. Mean outpatient visits PPY was 7.62 (95% CI: 6.81-8.49) compared with 6.60 (95% CI: 5.69-7.62) respectively. Average service provision PPY was \$3,520 for the No-ART group versus \$1,513 and \$964 for the HAART group for scenario 1 and 2, respectively, whereas the incremental cost per LYG was cost saving for both scenarios. In a sensitivity analysis based on the lower (25%) and upper (75%) interquartile range survival percentiles, the incremental cost per LYG ranged from \$1,557 to \$1,772 for the group without AIDS and from cost saving to \$111 for patients with AIDS. CONCLUSION: HAART is a cost-effective intervention in South Africa, and cost saving when HAART prices are further reduced. Our estimates, however, were based on direct costs, and as such the actual cost saving might have been underestimated if indirect costs were also included.

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Ekouevi DK, Toure R, Becquet R, Viho I, Sakarovitch C, Rouet F, Towne Gold B, Fassinou P, Leroy V, Blanche S, Dabis F. **Serum lactate levels in infants exposed peripartum to antiretroviral agents to prevent mother-to-child transmission of HIV: Agence Nationale de Recherches Sur le SIDA et les Hepatites Virales 1209 Study, Abidjan, Ivory Coast.** *Pediatrics* 2006;118(4):E1071-E1077.

Abstr. BACKGROUND. Mitochondrial toxicity was described in infants exposed to long-term antiretroviral regimens containing nucleoside analogues for the prevention of mother-to-child transmission of HIV. We measured the serum lactate levels in children born to HIV-1 infected African women receiving short-term antiretroviral prevention of mother-to-child transmission of HIV regimens. METHODS. A prospective study was conducted in women-child pairs from the third trimester of pregnancy to 3 months of life. The exposed group was formed by children exposed in utero to nucleoside analog antiretroviral regimens, zidovudine or zidovudine + lamivudine from 32 to 36 weeks of amenorrhea until delivery. All of these women received nevirapine single dose at the beginning of labor. The children received zidovudine during the first 7 days of life and a nevirapine single dose at day 3. The control group was formed by infants born to HIV-1-infected women who had received nevirapine single dose only and who were not exposed to nucleoside analog antiretroviral regimens. Serum lactate levels were measured at 4, 6, and 12 weeks of life by Cobas Integra 400. RESULTS. A total of 836 blood samples from 338 infants was collected (262 exposed and 76 controls). Median lactacidemia was 1.8 mmol/L (interquartile range: 1.2-2.7 mmol/L). Overall serum lactate levels ≥ 2.5 mmol/L, defining hyperlactatemia, were observed in 39 of the 292 infants who had ≥ 2 serum lactate measurements. The 3-month period prevalence of hyperlactatemia did not differ between the exposed group and the control group. All of the serum lactate levels returned to normal values in all of the subsequent samples. No case of symptomatic hyperlactatemia was detected during the study period. CONCLUSIONS. Increased lactate levels were identified equally in infants whose mother received short-term nucleoside analogs or nevirapine single dose for prevention of mother-to-child transmission of HIV. Although not rare, hyperlactatemia was not related to short-term exposure to nucleoside analog antiretroviral regimens.

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Hogg RS, Bangsberg DR, Lima VD, Alexander C, Bonner S, Yip B, Wood E, Dong WW, Montaner JS, Harrigan PR. **Emergence of Drug Resistance Is Associated with an Increased Risk of Death among Patients First Starting HAART.** *PLoS Medicine* 2006;3(9).

Abstr. BACKGROUND: The impact of the emergence of drug-resistance mutations on mortality is not well characterized in antiretroviral-naïve 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 naïve 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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Johnson MA, Gathe JC, Podzamczar D, Molina JM, Naylor CT, Chiu YL, King MS, Podsadecki TJ, Hanna GJ, Brun SC. **A once-daily lopinavir/ritonavir-based regimen provides noninferior antiviral activity compared with a twice-daily regimen.** Journal of Acquired Immune Deficiency Syndromes 2006;43(2):153-160.

Abstr. Objective: To evaluate the safety and noninferiority and to explore the efficacy of administration of once-daily versus twice-daily lopinavir/ritonavir (LPV/r) in antiretroviral-naive HIV-1-infected subjects. Design: Randomized, open-label, multicenter, comparative study. Methods: One hundred ninety anti retroviral-naive subjects with plasma HIV-1 RNA level > 1000 copies/mL and any CD4(+) cell count were randomized to lopinavir/ritonavir at a dose of 800/200 mg administered once daily (n = 115) or lopinavir/ritonavir at a dose of 400/100 mg administered twice daily (n = 75). Subjects also received tenofovir disoproxil fumarate (TDF) at a dose of 300 mg and emtricitabine (FTC) at a dose of 200 mg administered once daily. Results: The median baseline plasma HIV-1 RNA level and CD4(+) count were 4.8 log(10) copies/mL and 216 cells/mm(3), respectively. Before week 48, 20% (once daily) and 29% (twice daily) subjects discontinued. Virologic responses of the subjects through 48 weeks were comparable; 70% (once daily) and 64% (twice daily) achieved an HIV-1 RNA level < 50 copies/mL by intent-to-treat, noncompleter = failure analysis. No subject demonstrated LPV or TDF resistance, but 3 subjects (2 in the once-daily group, 1 in the twice-daily group) demonstrated FTC resistance. Mean increases in CD4(+) count were similar. Diarrhea (16% in the once-daily group, 5% in the twice-daily group; P = 0.036) was the most common moderate or severe study drug-related adverse event. Conclusions: Through 48 weeks, a once-daily regimen of lopinavir/ritonavir + TDF + FTC appears to have similar virologic and immunologic responses in antiretroviral-naive subjects as the same regimen with lopinavir/ritonavir administered twice daily. Both regimens were relatively well tolerated, and no LPV or TDF resistance was observed.

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Lopman BA, Barnabas RV, Boerma JT, Chawira G, Gaitskell K, Harrop T, Mason P, Donnelly CA, Garnett GP, Nyamukapa C, Gregson S. **Creating and validating an algorithm to measure AIDS mortality in the adult population using verbal autopsy.** PLoS Medicine 2006;3(8):e312.

Abstr. BACKGROUND: Vital registration and cause of death reporting is incomplete in the countries in which the HIV epidemic is most severe. A reliable tool that is independent of HIV status is needed for measuring the frequency of AIDS deaths and ultimately the impact of antiretroviral therapy on mortality. METHODS AND FINDINGS: A verbal autopsy questionnaire was administered to caregivers of 381 adults of known HIV status who died between 1998 and 2003 in Manicaland, eastern Zimbabwe. Individuals who were HIV positive and did not die in an accident or during childbirth (74%; n = 282) were considered to have died of AIDS in the gold standard. Verbal autopsies were randomly allocated to a training dataset (n = 279) to generate classification criteria or a test dataset (n = 102) to verify criteria. A rule-based algorithm created to minimise false positives had a specificity of 66% and a sensitivity of 76%. Eight predictors (weight loss, wasting, jaundice, herpes zoster, presence of abscesses or sores, oral candidiasis, acute respiratory tract infections, and vaginal tumours) were included in the algorithm. In the test dataset of verbal autopsies, 69% of deaths were correctly classified as AIDS/non-AIDS, and it was not necessary to invoke a differential diagnosis of tuberculosis. Presence of any one of these criteria gave a post-test probability of AIDS death of 0.84. CONCLUSIONS: Analysis of verbal autopsy data in this rural Zimbabwean population revealed a distinct pattern of signs and symptoms associated with AIDS mortality. Using these signs and symptoms, demographic surveillance data on AIDS deaths may allow for the estimation of AIDS mortality and even HIV prevalence.

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Maier M, Bwana M, Emenyonu N, Pepper L, Bangsberg DR. **How to Take HIV antiretroviral medications on time without a watch in rural Uganda.** PLoS Medicine 2006;3(3):e161.

Introduction. Castro has advocated that adherence to HIV antiretroviral therapy should be understood within a patient's clinical and social context. Over 90% of worldwide HIV infection occurs in resource-limited settings. Some have suggested that individuals living in extreme poverty may have difficulties with adherence to medication, including Andrew Natisios, who said Africans "don't know what Western time is". While recent reports suggest that adherence to HIV antiretroviral therapy in resource-limited settings may be as good as or better than resource-rich settings, the question remains: how do people take medications on time without a watch?

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Reis C, Heisler M, Amowitz LL, Moreland RS, Mafeni JO, Anyamele C, Iacopino V. **Discriminatory attitudes and practices by health workers toward patients with HIV/AIDS in Nigeria.** PLoS Medicine 2005;2(8):e246.

Abstr. BACKGROUND: Nigeria has an estimated 3.6 million people with HIV/AIDS and is home to one out of every 11 people with HIV/AIDS worldwide. This study is the first population-based assessment of discrimination against people living with HIV/AIDS in the health sector of a country. The purpose of this study was to characterize the nature and extent of discriminatory practices and attitudes in the health sector and indicate possible contributing factors and intervention strategies. The study involved a cross-sectional survey of 1,021 Nigerian health-care professionals (including 324 physicians, 541 nurses, and 133 midwives identified by profession) in 111 health-care facilities in four Nigerian states. METHODS AND FINDINGS: Fifty-four percent of the health-care professionals (550/1,021) were sampled from public tertiary care facilities. Nine percent of professionals reported refusing to care for an HIV/AIDS patient, and 9% indicated that they had refused an HIV/AIDS patient admission to a hospital. Fifty-nine percent agreed that people with HIV/AIDS should be on a separate ward, and 40% believed a person's HIV status could be determined by his or her appearance. Ninety-one percent agreed that staff and health-care professionals should be informed when a patient is HIV-positive so they can protect themselves. Forty percent believed that health-care professionals with HIV/AIDS should not be allowed to work in any area of health-care that requires patient contact. Twenty percent agreed that many with HIV/AIDS behaved immorally and deserve the disease. Basic materials needed for treatment and prevention of HIV were not adequately available. Twelve percent agreed that treatment of opportunistic infections in HIV/AIDS patients wastes resources, and 8% indicated that treating someone with HIV/AIDS is a waste of precious resources. Providers who reported working in facilities that did not always practice universal precautions were more likely to favor restrictive policies toward people with HIV/AIDS. Providers who reported less adequate training in HIV treatment and ethics were also more likely to report negative attitudes toward patients with HIV/AIDS. There was no consistent pattern of differences in negative attitudes and practices across the different health specialties surveyed. CONCLUSION: While most health-care professionals surveyed reported being in compliance with their ethical obligations despite the lack of resources, discriminatory behavior and attitudes toward patients with HIV/AIDS exist among a significant proportion of health-care professionals in the surveyed states. Inadequate education about HIV/AIDS and a lack of protective and treatment materials appear to contribute to these practices and attitudes.

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Ssali F, Stohr W, Munderi P, Reid A, Walker AS, Gibb DM, Mugenyi P, Kityo C, Grosskurth H, Hakim J, Byakwaga H, Katabira E, Darbyshire JH, Gilks CF. **Prevalence, incidence and predictors of severe anaemia with zidovudine-containing regimens in African adults with HIV infection within the DART trial.** *Antiviral Therapy* 2006;11 (6):741-749.

Abstr. Objective: To describe the prevalence, incidence and predictors of severe anaemia in previously untreated symptomatic HIV-infected adults with CD4(+) T-cells <200 cells/mm³ initiating zidovudine-containing regimens in Africa. Design: DART is a randomized trial comparing two strategies for HIV/AIDS management in Uganda and Zimbabwe. Methods: We analysed the occurrence of anaemia at weeks 4 and 12, and then every 12 weeks. We also evaluated sex, age, WHO stage, body mass index (BMI), baseline laboratory measurements and first regimen as predictors of developing grade 4 anaemia (<6.5 mg/dl) by week 48 using logistic regression. Results: To May 2005, 3,314 participants (65% women, 23% at WHO stage 4, median age=37 years, baseline CD4(+) T-cell=86 cells/mm³) and median baseline haemoglobin=11.4 g/dl had a median 72 weeks follow-up. Prevalence of grade 4 anaemia was 0.7%, 2.0%, 0.5% and <0.5% at weeks 4, 12, 24 and ≥ 36, respectively. Overall, 219 (6.6%) participants developed grade 4 anaemia by week 48; women and those with lower haemoglobin, CD4(+) T-cell count and BMI at baseline were at significantly higher risk (P<0.05), but not those with lower neutrophils or receiving cotrimoxazole at baseline. Conclusions: We observed a higher incidence of grade 4 anaemia than in studies from industrialized countries, which is likely to be due in part to population characteristics and in part to a higher rate of concurrent HIV-related clinical events. Clinical vigilance and haemoglobin measurements 4, 8 and 12 weeks after starting zidovudine could help to manage serious anaemia.

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