HIV Care & PMTCT in Resource-Limited Settings

Monthly Intelligence Report

Back Issues on Line

prepared by the Bordeaux Working Group

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**Abstr.** NA

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**Abstr.** Background: Although adherence to antiretroviral therapy may be higher in sub-Saharan Africa, knowledge regarding the magnitude of adherence needed to maintain virological Suppression in this setting is limited. Methods: A case-control Study among HIV-infected individuals initiating highly active antiretroviral therapy (HAART) in Gaborone, Botswana, was performed. Cases were randomly selected from subjects on HAART >= 6 months with plasma HIV-1 RNA levels (viral loads) >1000 copies/mL. Controls were randomly selected from subjects on HAART >= 6 months with all viral loads <400 copies/mL. HAART adherence was determined using pharmacy refill records. Results: In total, 302 individuals were included; 57 cases were compared with 245 controls with respect to adherence levels on nonnucleoside reverse transcriptase inhibitor-based HAART. Median adherence levels, as measured using pharmacy refill patterns, were consistently high but differed among cases and controls (91%, interquartile range 83%-97% for cases vs 97%, interquartile range 91%-100% for controls, P < 0.001, rank-sum test). Adherence <95% was independently associated with virological failure (odds ratio 4.19, 95% confidence interval 2.2 to 8.3). Conclusions: Very high rates of adherence were present in this setting, yet virological failure occurred nonetheless. Future work should explore other factors that might explain treatment failure in the setting of high levels of adherence.

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**Abstr.** Objective: To analyze the determinants of CD4 change in children during 3 periods: before highly active antiretroviral therapy (HAART), during the first year after HAART initiation, and past I year after HAART initiation. Methods: One hundred seventy-seven children enrolled in it prospective cohort in Abidjan received HAART during a mean follow-up of 30 months. A linear mixed-effects model was used for the first period, a mixed-effects piecewise model for the second period, and all asymptotic mixed-effects model for long-term CD4 dynamics. Results: Before HAART initiation, CD4 percentage decreased along time \[ \beta = -0.59 (-0.92 to -0.26) \] was positively associated with body mass index for age \[ \beta = 0.47 (0.22 to 0.72) \] and negatively associated with viral load \[ \beta = -1.01 (-1.90 to -0.13) \]. During the first year of treatment, the CD4 decrease reverted to a steep increase that was negatively associated with age at HAART initiation \[ \beta = -0.24 (-0.4 to -0.07) \] and with the mean viral load Under HAART \[ \beta = -1.51 (-2.21 to -0.81) \]. The long-term CD4 percentage was also negatively associated with the mean viral load under HAART \[ \beta = -4.97 (-6.21 to -3.72) \] and age at HAART initiation \[ \beta = -0.82 (-1.12 to -0.51) \]. Conclusions: Before HAART initiation, the CD4 cell percentage was associated with growth indicators whereas, after HAART, all early increase and a long-term plateau were negatively associated with the viral load and age at HAART initiation.

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Abstr. Access to highly active antiretroviral therapy (HAART) for persons infected with HIV in sub-Saharan Africa has greatly improved over the past few years. However, data on long-term clinical outcomes of Africans receiving HAART, patterns of HIV resistance to antiretroviral drugs and implications of HIV type-1 (HIV-1) subtype diversity in Africa for resistance, are limited. In resource-limited settings, concerns have been raised that deficiencies in health systems could create the conditions for accelerated development of resistance. Coordinated surveillance systems are being established to assess the emergence of resistance and the factors associated with resistance development, and to create the possibility for adjusting treatment guidelines as necessary. The purpose of this report is to review the literature on HIV-1 resistance to antiretroviral drugs in sub-Saharan Africa, in relation to the drug regimens used in Africa, HIV-1 subtype diversity and overall prevalence of resistance. The report focuses on resistance associated with treatment, prevention of mother-to-child transmission and transmitted resistance. It also outlines priorities for public health action and research.

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Abstr. Objective: To assess hematologic and hepatic toxicities associated with ill utero and breastfeeding exposure to maternal highly active antiretroviral therapy (HAART) among infants in Botswana. Design: A nested cohort Study within a randomized clinical trial (the Mashi Study). Laboratory toxicities among infants born to women who initiated HAART before delivery were compared with toxicities among those born to women who received zidovudine and a single close of nevirapine or placebo in labor. Infants were randomized to breastfeed with extended zidovudine or to formula-feed. Methods: Hemoglobin concentrations, absolute neutrophil and platelet Counts, and alanine aminotransferase and aspartate aminotransferase levels were recorded from birth to 7 months of age in infants. Grade 3 and 4 toxicities were compared by infant antiretroviral exposure status. Results: In-utero exposure to maternal HAART was associated with increased risk for neutropenia in infants Up to 1 month of age; 21.7% of HAART-exposed infants were neutropenic, compared with 5.5% of the infants exposed to zidovudine (P<0.01). However, neutropenia was no longer associated with antenatal exposure to HAART after 1 month of age. Postnatal exposure to HAART was not associated with hematologic or hepatic toxicities. Laboratory toxicities were clinically asymptomatic in all but one infant. Conclusion: Exposure to maternal HAART ill utero may increase the risk for infant neutropenia, particularly among breastfed infants, but the clinical significance of this finding is uncertain. The lack of association between exposure to HAART through breastfeeding and long-term toxicities in infants is reassuring but deserves study in larger cohorts. (C) 2008 Wolters Kluwer Health | Lippincott Williams and Wilkins.

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Abstr. Objective: To evaluate a treatment strategy of substituting zidovudine (ZDV) for stavudine (d4T)-based highly active antiretroviral therapy (HAART), aimed at preventing d4T-associated toxicity, in a programmatic setting in rural Cambodia. Methods: Survival probability, CD4 gain, anemia incidence, and factors associated with severe anemia were analyzed in a cohort of adult patients switched from d4T- to ZDV-containing regimens from March 2006 to March 2007. Results: Among 527 patients systematically switched to ZDV after d4T-based HAART for a median of 18 months, 4 (0.8%) patients died, 2 (0.4%) were lost to follow-up, 18 (3.4%) were transferred out, and 503 (95.4%) remained on HAART. Median CD4 gain was +263.5 cells/μL (interquartile range: 89.25-369.5) at 24 months. Within 1 year after the switch, 21.9% and 7.1% of patients developed anemia (grades 1-4) and severe anemia (grades 3-4), respectively. Low body mass index (<= 18) and low CD4 count (<200 cells/μL) at the time of switch were factors associated with severe anemia. Additional follow-up visits for laboratory monitoring and adherence counseling, increased absenteeism from work, and transportation costs for the patients were noted. Conclusions: The switch strategy of substituting ZDV for d4T-based HAART led to satisfactory overall clinical outcomes. However, it resulted in a relatively high incidence of mild to severe anemia and increased burden for the program and the patients.

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Abstr. In a retrospective cohort analysis, loss to follow-up and mortality rates were compared between pregnant and nonpregnant women referred to a community-based antiretroviral treatment program in South Africa. Although there was no significant difference in adjusted mortality rates between the two groups, the pregnant women had a substantially higher risk of loss to follow-up both pretreatment and on-treatment. This finding highlights the need for programmatic interventions to address retention in care for this patient population.

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Abstr. Background Efavirenz is used for the antiretroviral treatment of HIV/tuberculosis-coinfected patients in developing countries. A switch to nevirapine is regularly carried out because of the cost and side effects of efavirenz. Pharmacokinetic studies suggested that nevirapine should be initiated at full dose when used as a substitute for efavirenz. Objectives The aim of this study was to measure the cumulative incidence of adverse events (AEs) related to nevirapine in patients switched from efavirenz to immediate full-dose nevirapine (FDN). Methods In 2001 an antiretroviral treatment programme was initiated with the first-line regimen stavudine, lamivudine and efavirenz. In 2003, the fixed-dose combination of stavudine, lamivudine and nevirapine was recommended. Thus, first-line therapy was changed and FDN was initiated when patients were switched from efavirenz to nevirapine. Results Between April and December 2004, 394 patients were switched from efavirenz to FDN. The cumulative incidence of AEs related to nevirapine was 13.2% [95% confidence interval (CI) 10.2-16.7] and that of severe AEs was 8.9% (95% CI 6.5-11.9). In women the incidence of AEs was 17.6% (95% CI 12.1-
Conclusions: Our results indicate that an FDN switch from efavirenz does not appear to result in more AEs than when nevirapine is initiated with escalating doses. These data are particularly relevant in resource-limited settings.

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Little KE, Bland RM, Newell ML. **Vertically acquired paediatric HIV infection: the challenges of providing comprehensive packages of care in resource-limited settings.** Tropical Medicine and International Health 2008;13(9):1098-1110.

**Abstr.** The successes achieved in paediatric disease management in well-resourced countries in recent years highlight the vast divide between the care options, and ultimately survival, between developed and developing areas of the world. Using an extensive literature review, we quantify recent achievements in terms of improved survival and quality of life, and examine current evidence of the effects of treatment on the survival and morbidity of HIV-infected children in developing countries. When provided with the same care as their counterparts in developed countries, children in developing countries show similar improvements in survival and general health, with 1-year survival rates exceeding 90% in many African settings. Despite the challenges of providing comprehensive packages of care in resource-limited settings, there is an urgent need to scale up prevention and treatment of HIV infections in children, focussing on strengthening Prevention of Mother-to-Child Transmission programmes in order to reduce the numbers of infants who are infected in addition to reducing morbidity and mortality among their mothers.

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**Abstr.** Roll-out of antiretroviral treatment (ART) raises concerns about the potential for unprotected sex if sexual activity increases with well-being, resulting in continued HIV spread. Beliefs about reduced risk for HIV transmission with ART may also influence behavior. From September 2003 to November 2004, 234 adults enrolled in a trial assessing the efficacy of modified directly observed therapy in improving adherence to ART. Unsafe sexual behavior (unprotected sex with an HIV-negative or unknown status partner) before starting ART and 12 months thereafter was compared. Participants were a mean 37.2 years (standard deviation [SD] = 7.9 years) and 64%, (149/234) were female. Nearly half (107/225) were sexually active in the 12 months prior to ART, the majority (96/107) reporting one sexual partner. Unsafe sex was reported by half of those sexually active in the 12 months before ART (54/107), while after 12 months ART, this reduced to 28%, (30/107). Unsafe sex was associated with nondisclosure of HIV status to partner; recent HIV diagnosis; not being married or cohabiting; stigma; depression and body mass index < 18.5kg/m(2). ART beliefs, adherence, and viral suppression were not associated With unsafe sex. After adjusting for gender and stigma, unsafe sex was 0.59 times less likely after 12 months ART than before initiation (95% confidence interval [CI] = 0.37-0.94; p = 0.026). In conclusion, although risky sexual behaviors had decreased, a considerable portion do not practice safe sex. Beliefs about ART’s effect on transmission, viral load, and adherence appear not to influence sexual behavior but require long-term surveillance. Positive prevention interventions for those receiving ART must reinforce safer sex practices and partner disclosure.

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Abstr. Background HIV-infected children have a lower seroconversion rate to hepatitis B virus (HBV) immunization than healthy children. Previous studies have produced conflicting results on CD4 cell counts as predictors of vaccine response. No study has evaluated the response rate to HBV vaccination in HIV-infected children receiving highly active antiretroviral therapy (HAART). Our aim was to vaccinate HIV-infected children living in a close community and to investigate the anamnestic response rate after vaccination with its predictors. Methods Eighty-four HIV-positive children aged 1-10 years who were negative for antibodies to the HBV core antigen (anti-HBc) completed immunization with three doses of 5 g HBVAXPRO (Aventis, Milan, Italy). Quantitative testing for antibodies to the HBV surface antigen (anti-HBs) was performed: a seroprotective titre was defined as anti-HBs > 10 mUI/mL. Results After the vaccination, the anti-HBs seroconversion rate was 59.5%. It was higher in individuals in Centers for Disease Control and Prevention (CDC) immune category 1 than in those in CDC categories 2 and 3. Seroconversion was found in 70.8% of HAART-treated and 44.4% of treatment-naive children. In multivariable models, HAART use and absolute CD4 cell counts were independently associated with probability of seroconversion and with higher anti-HBs titles. Conclusions We found a higher seroconversion rate compared with previous studies in HIV-infected children. In children who are candidates to receive antiretroviral therapy, it may be advisable to defer HBV vaccination until after treatment initiation.

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Abstr. Background: The long-term maintenance of antiretroviral therapy (ART) remains an important issue, especially in limited-resource settings where additional barriers exist. A cross-sectional study was performed 24 months after ART initiation for patients treated in Cambodia in order to estimate the prevalence and identify determinants of non-adherence. Methods: Adults receiving ART for 24 2 months were considered eligible for the study. Self-reported nonadherence was defined according to an algorithm based on six items. The questionnaire also assessed ART-related side effects and HIV disclosure. HIV-1 RNA plasma viral load was measured using real-time PCR Multivariate rare events logistic regression analysis was used to identify independent factors associated with non-adherence. Results: A total of 346 patients participated in the study. At 24 months, 95% of patients were adherent, 80% had HIV RNA < 40 copies/ml and 75% had CD4(+) T-cell counts > 200 cells/mm(3). Virological success was significantly higher in adherent patients than in non-adherent patients (81% versus 56%, P=0.021). Living in a rural area, limited HIV disclosure and perceived lipodystrophy were independently associated with non-adherence. Conclusions: At 24 months, adherence to ART was high and explained positive virological outcomes. In order to maintain adherence and long-term virological benefits, special attention should be given to patients living in rural areas, those with lipodystrophy-related symptoms and others who express difficulties disclosing their condition to close family members.

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**Abstr.** Background: The aim of this study was to examine factors influencing plasma concentration of efavirenz and nevirapine. Methods: Data from the Liverpool Therapeutic Drug Monitoring (TDM) registry were linked with the UK Collaborative HIV Cohort (CHIC) Study. For each patient, the first measurement of efavirenz (600 or 800 mg/day) or nevirapine (400 mg/day) plasma concentration was included. Linear regression was used to evaluate the association of dose, gender, age, weight, ethnicity and concomitant antiretroviral drugs or rifampicin with log-transformed drug concentration, adjusted for time since last intake. Results: Data from 339 patients on efavirenz (34% black, 17% rifampicin) and 179 on nevirapine (27% black, 6% rifampicin) were included. Multivariable models revealed the following predictors for efavirenz concentration: black ethnicity (59% higher; P < 0.001), weight (10% lower per additional 10 kg; P=0.002), 800 mg/day (52% higher; P=0.027), rifampicin (35% lower; P=0.039), and zidovudine (25% lower; P=0.010). Notably, without adjustment for other factors, patients on rifampicin had 48% higher efavirenz concentration, as these patients were mostly black and on 800 mg/day. For nevirapine the predictors were black ethnicity (39% higher; P=0.002), rifampicin (40% lower; P=0.002), protease inhibitor (28% higher; P=0.008) and tenofovir (22% higher; P=0.024). Conclusions: We observed clear associations between ethnicity and concentrations of nevirapine and efavirenz. Our analyses confirm that concomitant rifampicin substantially decreases concentration of both efavirenz and nevirapine; however, for efavirenz this effect was more than counterbalanced by the effect of ethnicity and increased efavirenz dose. There was also an additional impact of weight, which should be considered when determining optimal dosage. Other associations from our analysis (between tenofovir or protease inhibitor and nevirapine, and zidovudine and efavirenz), require confirmation in formal pharmacokinetic studies.

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**Abstr.** Background. Few prospective studies have measured survival rates among human immunodeficiency virus (HIV)-infected children in sub-Saharan Africa prior to the availability of antiretroviral therapy. Methods. In the context of an observational study of the immunogenicity of measles vaccine in Zambia, we prospectively followed up children from approximately 9 months of age and assessed survival rates, risk factors for mortality, and circumstances at the time of death according to HIV-infection or HIV-exposure status. Results. There were 56 deaths among 492 study children during follow-up to 3 years of age. Thirty-nine percent of the 105 children with HIV infection died during the study period, compared with 5.0% of the 260 HIV-seropositive but uninfected children and 1.6% of the 127 HIV-seronegative children. Estimated survival probabilities from 9 through 36 months of age were 52% among HIV-infected children, 95% among initially HIV-seropositive but uninfected children, and 98% among HIV-seronegative children. In multivariable analyses, history of a clinic visit within the 4 weeks prior to study entry (adjusted hazard ratio, 4.6; 95% confidence interval, 1.5-13.5), hemoglobin level <8 g/dL at study entry (adjusted hazard ratio, 4.4; 95% confidence interval, 1.5-12.6), land CD4(+) T lymphocyte percentage <15% at study entry (adjusted hazard ratio, 3.2; 95% confidence interval, 1.1-9.5) were associated with mortality among HIV-infected children. Conclusions. Only approximately one-half of HIV-infected Zambian children who were alive at 9 months of age survived to 3 years of age, supporting the
urgent need for the prevention of mother-to-child transmission of HIV and the early diagnosis and treatment of HIV infection in children in sub-Saharan Africa.

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Abstr. Objective: Determine the pattern of drug resistance among HIV infected drug exposed patients failing therapy in Ouagadougou, Burkina Faso. Methods: The protease (PR) and reverse transcriptase (RT) of 87 samples from 75 treatment exposed HIV infected patients failing therapy were PCR amplified, sequenced, subtyped and analyzed for the presence of drug resistance mutations. Results: The most common drugs used were 3TC, AZT (or d4T) and EFV. The dominant subtypes were CRF06-cpx (48%) and CRF02_AG (40%). The prevalence of resistance mutations among patients failing therapy was: PR inhibitors (PI), 40%; non-nucleoside RT-inhibitors (NNRTI) 76% and nucleoside RT-inhibitors (NRTI), 85%. Dominant mutations included M461 (37%), 154V (26%), V82A/T/F (30%) in PR; K103N (44%), G190A/S (16%) and T215F/Y (48%) (NRTIs) in RT. Some resistance mutations, notably R67N/G, K70R and L210W (thymidine analogue mutations-TAMs); K101E, V179E in RT, 154V, V82A/T/F and L90M in PR were significantly higher among CRF06-cpx than CRF02_AG strains (P < 0.05). Although not significant, other TAMs (M41L, T215F/Y, K219Q/E) also occurred more frequently among CRF06-cpx strains as well. Conclusion: There is a high prevalence of drug resistance mutations among ARV exposed patients in Burkina Faso with an unexpected subtype-specific difference. Validation of this result will require larger sample sizes and in vitro drug susceptibility studies with CRF06-cpx strains.

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Abstr. Objective: Several co-infections have been shown to impact the progression of HIV-1 infection. We sought to determine if treatment of helminth co-infection in HIV-1-infected adults impacted markers of HIV-1 disease progression. Design: To date, there have been no randomized trials to examine the effects of soil-transmitted helminth eradication on markers of HIV-1 progression. Methods: A randomized, double-blind, placebo-controlled trial of albendazole (400 mg daily for 3 clays) in antiretroviral-naive HIV-1-infected adults (CD4 cell count >200 cells/μl) with soil-transmitted helminth infection was conducted at 10 sites in Kenya (Clinical Trials.gov NCT00130910). CD4 and plasma HIV-1 RNA levels at 12 weeks following randomization were compared in the trial arms Using linear regression, adjusting for baseline values. Results: Of 1551 HIV-1-infected individuals screened for helminth infection, 299 were helminth infected. Two hundred and thirty-four adults were enrolled and Underwent randomization and 208 individuals Were included in intent-to-treat analyses. Mean CD4 cell count was 557 cells/μl and mean plasma viral load was 4.75 log₁₀ copies/ml at enrollment. Albendazole therapy resulted in significantly higher CD4 cell counts among individuals with Ascaris lumbricoides infection after 12 weeks of follow-up (+109cells/μl; 95% confidence interval +38.9 to +179.0, P=0.003) and a trend for 0.54 log₁₀ lower HIV-1 RNA levels (P=0.09). These effects were not seen with treatment of other species of soil-transmitted helminths. Conclusion: Treatment of A. lumbricoides with albendazole in HIV-1-coinfected adults resulted in significantly increased CD4 cell counts during 3-
month follow-up. Given the high prevalence of A. lumbricoides infection worldwide, deworming may be all important potential strategy to delay HIV-1 progression.

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Abstr. Background. In China, many former plasma donors were infected with the human immunodeficiency virus (HIV) in the early-mid-1990s. Highly active antiretroviral therapy (HAART) was provided for former plasma donors beginning in 2002. The effect of HAART on mortality in this cohort has not been described. Methods. This study is a retrospective analysis of the national HIV epidemiology and treatment databases for the period 1993-2006. All HIV-infected subjects from 10 counties with a high prevalence of HIV infection in 6 provinces were eligible. Inclusion criteria were: (1) history of plasma donation, (2) positive Western blot result, (3) clinical diagnosis of AIDS or CD4(+) cell count <200 cells/μL at any time, and (4) age ≥ 18 years at AIDS diagnosis. Results. Of 9059 eligible subjects, 4093 met the inclusion criteria. Mean age was 41 years, 51% were male, 99% were farmers, and 87% were from Henan Province. Overall mortality decreased from 27.3 deaths per 100 person-years in 2001 to 4.6 deaths per 100 person-years in 2006. Conversely, the percentage of patient-years receiving HAART increased from 0% in 2001 to 70.5% in 2006. In a multivariate Cox proportional hazards analysis, not receiving HAART was the greatest risk factor for mortality (hazard ratio, 2.8; 95% confidence interval, 2.4-3.3). Among treated patients, those who had lower CD4(+) cell counts and higher numbers of opportunistic infections at the initiation of therapy were at greater risk of death. Conclusions. The national treatment program has significantly reduced the mortality rate among HIV-infected former plasma donors through the use of generic drugs in a rural treatment setting with limited laboratory monitoring. Treatment success can be improved through increased coverage and earlier initiation of therapy.

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Abstr. Even after 25 years of experience, HIV prevention programming remains largely deficient. We identify four areas that managers of national HIV prevention programmes should reassert and hence refocus their efforts—improvement of targeting, selection, and delivery of prevention interventions, and optimisation of funding. Although each area is not wholly independent from one another, and because each country and epidemic context will require a different balance of time and funding allocation in each area, we present the current state of each dimension in the global HIV prevention arena and
propose practical ways to remedy present deficiencies. Insufficient data for intervention effectiveness and country-specific epidemiology has meant that programme managers have operated, and continue to operate, in a fog of uncertainty. Although priority must be given to the improvement of prevention methods and the capacity for the generation and use of evidence to improve programme planning and implementation, uncertainty will remain. In the meantime, however, we argue that prevention programming can be made much more effective by use of information that is readily available.

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Abstr. This paper makes five key points. First is that the aggregate effect of radical and sustained behavioural changes in a sufficient number of individuals potentially at risk is needed for successful reductions in HIV transmission. Second, combination prevention is essential since HIV prevention is neither simple nor simplistic. Reductions in HIV transmission need widespread and sustained efforts, and a mix of communication channels to disseminate messages to motivate people to engage in a range of options to reduce risk. Third, prevention programmes can do better. The effect of behavioural strategies could be increased by aiming for many goals (e.g., delay in onset of first intercourse, reduction in number of sexual partners, increases in condom use, etc) that are achieved by use of multilevel approaches (e.g., couples, families, social and sexual networks, institutions, and entire communities) with populations both uninfected and infected with HIV. Fourth, prevention science can do better. Interventions derived from behavioural science have a role in overall HIV-prevention efforts, but they are insufficient when used by themselves to produce substantial and lasting reductions in HIV transmission between individuals or in entire communities. Fifth, we need to get the simple things right. The fundamentals of HIV prevention need to be agreed upon, funded, implemented, measured, and achieved. That, presently, is not the case.

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Abstr. Recognition that social, economic, political, and environmental factors directly affect HIV risk and vulnerability has stimulated interest in structural approaches to HIV prevention. Progress in the use of structural approaches has been limited for several reasons: absence of a clear definition; lack of operational guidance; and limited data on the effectiveness of structural approaches to the reduction of HIV incidence. In this paper we build on evidence and experience to address these gaps. We begin by defining structural factors and approaches. We describe the available evidence on their effectiveness and discuss methodological challenges to the assessment of these often complex efforts to reduce HIV risk and vulnerability. We identify core principles for implementing this kind of work. We also provide recommendations for ensuring the integration of structural approaches as part of combined prevention strategies.

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Abstr. Intensive research efforts for more than two decades have not yet resulted in an HIV vaccine of even moderate effectiveness. However, some progress has been made with other biomedical interventions, albeit on the basis of inconsistent levels of evidence. The male condom, if used correctly and consistently, has been proven in observational
studies to be very effective in blocking HIV transmission during sexual intercourse; and, in three randomised trials, male circumcision was protective against HIV acquisition among men. Treatment of sexually transmitted infections, a public health intervention in its own right, has had mixed results, depending in part on the epidemic context in which the approach was assessed. Finally, oral and topical antiretroviral compounds are being assessed for their role in reduction of HIV transmission during sexual intercourse. Research on biomedical interventions poses formidable challenges. Difficulties with product adherence and the possibility of sexual disinhibition are important concerns. Biomedical interventions will need to be part of an integrative package that includes biomedical, behavioural, and structural interventions. Assessment of such multicomponent approaches with moderate effects is difficult. Issues to be considered include the nature of control groups and the effect of adherence on the true effectiveness of the intervention.

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**Abstr.** A quarter of a century of AIDS responses has created a huge body of knowledge about HIV transmission and how to prevent it, yet every day, around the world, nearly 7000 people become infected with the virus. Although HIV prevention is complex, it ought not to be mystifying. Local and national achievements in curbing the epidemic have been myriad, and have created a body of evidence about what works, but these successful approaches have not yet been fully applied. Essential programmes and services have not had sufficient coverage; they have often lacked the funding to be applied with sufficient quality and intensity. Action and funding have not necessarily been directed to where the epidemic is or to what drives it. Few programmes address vulnerability to HIV and structural determinants of the epidemic. A prevention constituency has not been adequately mobilised to stimulate the demand for HIV prevention. Confident and unified leadership has not emerged to assert what is needed in HIV prevention and how to overcome the political, sociocultural, and logistic barriers in getting there. We discuss the combination of solutions which are needed to intensify HIV prevention, using the existing body of evidence and the lessons from our successes and failures in HIV prevention.

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