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Discrimination against groups at high risk of contracting HIV and those already infected is hampering prevention and treatment in the Middle East and North Africa. Enlisting the help of influential religious leaders will be key in addressing the problem, say experts. Jan McGirk reports. Unless Middle Eastern and North African countries can tackle social taboos and homophobia, they cannot keep their adult prevalence of HIV/AIDS at its current comparatively low rate, say experts. Regional health authorities are alarmed that the most vulnerable Arab patients often avoid or delay seeking medical services due to shame or fear that they will be “outed”, humiliated, shunned, deported, or jailed. Any notion that Arab countries have escaped the global HIV/AIDS epidemic—perhaps due to religious strictures on sexual behaviour—is dispelled by the UN’s latest statistics, released in mid-November, 2007. Last year, HIV/AIDS-related diseases killed at least 25000 people in this strategic region which stretches from the Maghreb, beyond the eastern Mediterranean and down to the Horn of Africa, and at least 35 000 people were newly infected with HIV. People younger than 25 years make up half these new cases. The total number of people living with HIV/AIDS in the Middle East and North Africa now is estimated at between 38000 and half a million. Currently, some 0·3% of adults are infected with HIV in the Arab world. In Sudan, however, the rate is more than five times this average.


After weeks of negotiations, the US Senate has authorised the President’s Emergency Plan for AIDS Relief (PEPFAR). The new bill has been hailed a substantial achievement by many in the global-health community, but some critics say that it does not go far enough. Nellie Bristol reports. The USA is set to approve a 5-year US$48 billion global-health bill that reauthorises and broadens the scope of the President’s Emergency Plan for AIDS Relief (PEPFAR). In addition to outlining continued funding for HIV/AIDS treatment, care, and prevention in high-prevalence countries, the new legislation more explicitly addresses social drivers of the epidemic and bolsters health systems. The Senate approved the bill on July 16 on an 80–16 vote. Final approvals by Congress and President George Bush are expected to follow shortly. PEPFAR could receive up to $37 billion in funds between the fiscal years 2009 and 2013 under the measure. In the same period, the bill allows $4 billion for activities to combat tuberculosis globally and $5 billion for anti-malaria initiatives. The Global Fund to Fight AIDS, Tuberculosis and Malaria is slated to receive $2 billion in fiscal year 2009.


Although treatments for Alzheimer's disease sometimes improve cognition, functional ability, or behaviour compared with baseline levels, such improvements are inconsistent across studies and measures, and effects diminish over time. More effective treatments are needed. We assessed the safety, tolerability, and efficacy of dimebon in the treatment of patients with mild-to-moderate Alzheimer's disease. We enrolled 183 patients with mild-to-moderate Alzheimer's disease (mini-mental state examination [MMSE] scores 10–24) at 11 sites in Russia. Patients were randomly assigned by a computer-generated randomisation scheme to receive oral dimebon, 20 mg three times a day (60 mg/day [n=89]), or matched placebo (n=94). Other antidepressants were not allowed. The primary outcome measure assessed cognition, the difference in mean change from baseline to week 26, or last completed observation on the cognitive subscale of the Alzheimer's disease assessment scale (ADAS-cog). All patients and study personnel were blinded throughout the study. We
compared dimebon with placebo with an intention-to-treat analysis, with last observation carried forward (ITT-LOCF) imputation. Analyses were repeated on the fully evaluable population, defined as all patients in the intention-to-treat population who had an ADAS-cog at week 26 and at least 80% compliance. 134 patients (68 in dimebon group, 66 in placebo group) enrolled in the 6-month blinded extension phase of the study. 155 (85%) patients completed the trial (78 [88%] in dimebon group, 77 [82%] in placebo group). Treatment with dimebon resulted in significant benefits in ADAS-cog compared with placebo (ITT-LOCF) at week 26 (mean drug-placebo difference -4.0 [95% CI -5.73 to -2.28]; p<0.0001). Results of the ITT-LOCF and the evaluable population analyses were much the same for all measures. Patients given dimebon were significantly improved over baseline for ADAS-cog (mean difference -1.9 [-2.92 to -0.85]; p=0.0005). Dimebon was well tolerated: dry mouth and depressed mood or depression were the most common adverse events associated with dimebon (12 [14%] patients for each symptom by week 26). The percentage of patients who had adverse events in the two groups did not differ. Dimebon was safe, well tolerated, and significantly improved the clinical course of patients with mild-to-moderate Alzheimer’s disease.


Immunisation of patients with Alzheimer’s disease with full-length amyloid-à peptide (Aâ42) can clear amyloid plaques from the brain. Our aim was to assess the relation between Aâ42 immune response, degree of plaque removal, and long-term clinical outcomes. In June, 2003, consent for long-term clinical follow-up, post-mortem neuropathological examination, or both, was sought from 80 patients (or their carers) who had entered a phase I randomised, placebo-controlled trial of immunisation with Aâ42 (AN1792, Elan Pharmaceuticals) in September, 2000. The follow-up study was completed in September, 2006. Plaques were assessed in terms of the percentage area of the cortex with Aâ immunostaining (Aâ load) and in terms of characteristic histological features reflecting plaque removal. Survival of all 80 individuals until severe dementia or death was assessed with a Cox proportional hazard model. 20 participants—15 in the AN1792 group, five in the placebo group—died before follow-up started. A further 22 patients—19 in the AN1792 group, three in the placebo group—died during follow-up. Nine of the deceased patients, all in the AN1792 group, had given consent for post-mortem analysis; one of these who did not die with Alzheimer’s disease was excluded. In the remaining eight participants who received immunisation and who were examined neuropathologically, mean Aâ load was lower than in an unimmunised control group that was matched for age at death (2.1% [SE 0.7] in treated participants vs 5.1% [0.9] in controls; mean difference 3.0%, 95% CI 0.6—5.4; p=0.02). Although there was considerable variation in Aâ load and degree of plaque removal among immunised participants, the degree of plaque removal varied significantly with mean antibody response attained during the treatment study period (Kruskal-Wallis p=0.02). Seven of the eight immunised patients who underwent post-mortem assessment, including those with virtually complete plaque removal, had severe end stage dementia before death. In the whole cohort, there was no evidence of improved survival (hazard ratio 0.93, 95% CI 0.43—3.11; p=0.86) or of an improvement in the time to severe dementia (1.18, 0.45—3.11; p=0.73) in the AN1792 group versus the placebo group. Although immunisation with Aâ42 resulted in clearance of amyloid plaques in patients with Alzheimer’s disease, this clearance did not prevent progressive neurodegeneration.

Whether lipoproteins are better markers than lipids and lipoproteins for coronary heart disease is widely debated. Our aim was to compare the apolipoproteins and cholesterol as indices for risk of acute myocardial infarction. We did a large, standardised case-control study of acute myocardial infarction in 127,461 cases and 147,637 age-matched (plus or minus 5 years) and sex-matched controls in 52 countries. Non-fasting blood samples were available from 9345 cases and 127,120 controls. Concentrations of plasma lipids, lipoproteins, and apolipoproteins were measured, and cholesterol and apolipoprotein ratios were calculated. Odds ratios (OR) and 95% CI, and population-attributable risks (PARs) were calculated for each measure, overall and by ethnic group by comparison of the top four quintiles with the lowest quintile. The apolipoprotein B100 (ApoB)/apolipoprotein A1 (ApoA1) ratio had the highest PAR (54%) and the highest OR with each 1 SD difference (1.59, 95% CI 1.53—1.64). The PAR for ratio of LDL cholesterol/HDL cholesterol was 37%. PAR for total cholesterol/HDL cholesterol was 32% which was substantially lower than that of the ApoB/ApoA1 ratio (p=0.0001). These results were consistent in all ethnic groups, men and women, and for all ages. The non-fasting ApoB/ApoA1 ratio was superior to any of the cholesterol ratios for estimation of the risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages, and it should be introduced into worldwide clinical practice. Canadian Institutes of Health Research, the Heart and Stroke Foundation of Ontario, the InternationaClinical Epidemiology Network
UNICEF/WHO recommends that infants born to HIV-infected mothers who do not have access to acceptable, feasible, affordable, sustainable, and safe replacement feeding should be exclusively breastfed for at least 6 months. The aim of three trials in Ethiopia, India, and Uganda was to assess whether daily nevirapine given to breastfed infants through 6 weeks of age can decrease HIV transmission via breastfeeding. HIV-infected women breastfeeding their infants were eligible for participation. Participants were randomly assigned to receive either single-dose nevirapine (nevirapine 200 mg to women in labour and nevirapine 2 mg/kg to newborns after birth) or 6 week extended-dose nevirapine (nevirapine 200 mg to women in labour and nevirapine 2 mg/kg to newborn babies after birth plus nevirapine 5 mg daily from days 8-42 for the infant). The randomisation sequences were generated by computer at a central data coordinating centre. The primary endpoint was HIV infection at 6 months of age in infants who were HIV PCR negative at birth. Analyses were by modified intention to treat, excluding infants with missing specimens and those with indeterminate or confirmed HIV infection at birth. 2024 liveborn infants randomised in the study had at least one specimen tested before 6 months of age (1047 infants in the single-dose group and 977 infants in the extended-dose group). The modified intention-to-treat population included 986 infants in the single-dose group and 901 in the extended-dose group. At 6 months, 87 children in the single-dose group and 62 in the extended-dose group were infected with HIV (relative risk 0.80, 95% CI 0.58-1.10; p=0.16). At 6 weeks of age, 54 children in the single-dose group and 25 in the extended-dose group were HIV positive (0.54, 0.34-0.85; p=0.009). 393 infants in the single-dose group and 346 in the extended-dose group experienced grade 3 or 4 serious adverse events during the study (p=0.54). Although a 6-week regimen of daily nevirapine might be associated with a reduction in the risk of HIV transmission at 6 weeks of age, the lack of a significant reduction in the primary endpoint—risk of HIV transmission at 6 months—suggests that a longer course of daily infant nevirapine to prevent HIV transmission via breast milk might be more effective where access to affordable and safe replacement feeding is not yet available and where the risks of replacement feeding are high.


Combination antiretroviral therapy has led to significant increases in survival and quality of life, but at a population-level the effect on life expectancy is not well understood. Our objective was to compare changes in mortality and life expectancy among HIV-positive individuals on combination antiretroviral therapy. The Antiretroviral Therapy Cohort Collaboration is a multinational collaboration of HIV cohort studies in Europe and North America. Patients were included in this analysis if they were aged 16 years or over and antiretroviral-naive when initiating combination therapy. We constructed abridged life tables to estimate life expectancies for individuals on combination antiretroviral therapy in 1996–99, 2000–02, and 2003–05, and stratified by sex, baseline CD4 cell count, and history of injecting drug use. The average number of years remaining to be lived by those treated with combination antiretroviral therapy at 20 and 35 years of age was estimated. Potential years of life lost from 20 to 64 years of age and crude mortality rates were also calculated. 180587, 137914, and 107854 eligible patients initiated combination antiretroviral therapy in 1996–99, 2000–02, and 2003–05, respectively. 2056 (4.7%) deaths were observed during the study period, with crude mortality rates decreasing from 16.3 deaths per 1000 person-years in 1996–99 to 10.0 deaths per 1000 person-years in 2003–05. Potential years of life lost per 1000 person-years also decreased over the same time, from 366 to 189 years. Life expectancy at age 20 years increased from 36.1 (SE 0.6) years to 49.4 (0.5) years. Women had higher life expectancies than did men. Patients with presumed transmission via injecting drug use had lower life expectancies than did those from other transmission groups (32.6 [1.1] years vs 47.7 [0.3] years in 2003–05). Life expectancy was lower in patients with lower baseline CD4 cell counts than in those with higher baseline counts (32.4 [1.1] years for CD4 cell counts below 100 cells per μL vs 50.4 [0.4] years for counts of 200 cells per μL or more). Life expectancy in HIV-infected patients treated with combination antiretroviral therapy increased between 1996 and 2005, although there is considerable variability between subgroups of patients.


A consensus statement released on behalf of the Swiss Federal Commission for HIV/AIDS suggests that people receiving effective antiretroviral therapy—ie, those with undetectable plasma HIV RNA (<40 copies per mL)—are sexually non-infectious. We analysed the implications of this statement at a population level. We used a simple
mathematical model to estimate the cumulative risk of HIV transmission from effectively treated HIV-infected patients (HIV RNA <10 copies per mL) over a prolonged period. We investigated the risk of unprotected sexual transmission per act and cumulatively over many exposures, within couples initially discordant for HIV status. Assuming that each couple had 100 sexual encounters per year, the cumulative probability of transmission to the serodiscordant partner each year is 0.0022 (uncertainty bounds 0.0008–0.0058) for female-to-male transmission, 0.0043 (0.0016–0.0115) for male-to-female transmission, and 0.043 (0.0159–0.1097) for male-to-male transmission. In a population of 107,000 serodiscordant partnerships, over 10 years the expected number of seroconversions would be 215 (80–564) for female-to-male transmission, 425 (159–1096) for male-to-female transmission, and 3524 (1477–6871) for male-to-male transmission, corresponding to an increase in incidence of four times compared with incidence under current rates of condom use. Our analyses suggest that the risk of HIV transmission in heterosexual partnerships in the presence of effective treatment is low but non-zero and that the transmission risk in male homosexual partnerships is high over repeated exposures. If the claim of non-infectiousness in effectively treated patients was widely accepted, and condom use subsequently declined, then there is the potential for substantial increases in HIV incidence.

**SEMINAR**


Polymyalgia rheumatica and giant-cell arteritis are closely related disorders that affect people of middle age and older. They frequently occur together. Both are syndromes of unknown cause, but genetic and environmental factors might have a role in their pathogenesis. The symptoms of polymyalgia rheumatica seem to be related to synovitis of proximal joints and extra-articular synovial structures. Giant-cell arteritis primarily affects the aorta and its extracranial branches. The clinical findings in giant-cell arteritis are broad, but commonly include visual loss, headache, scalp tenderness, jaw claudication, cerebrovascular accidents, aortic arch syndrome, thoracic aorta aneurysm, and dissection. Glucocorticosteroids are the cornerstone of treatment of both polymyalgia rheumatica and giant-cell arteritis. Some patients have a chronic course and might need glucocorticosteroids for several years. Adverse effects of glucocorticosteroids affect more than 50% of patients. Trials of steroid-sparing drugs have yielded conflicting results. A greater understanding of the molecular mechanisms involved in the pathogenesis should provide new targets for therapy.

**REVIEW**


This Review discusses physiological, emotional, behavioural, and cognitive aspects of psychological adjustment to chronic illness. Reviewing the reports of the past decade, we identify four innovative and promising themes that are relevant for understanding and explaining psychological adjustment. In particular, the emphasis on the reasons why people fail to achieve a healthy adjustment has shifted to the identification of factors that help patients make that adjustment. To promote psychological adjustment, patients should remain as active as is reasonably possible, acknowledge and express their emotions in a way that allows them to take control of their lives, engage in self-management, and try to focus on potential positive outcomes of their illness. Patients who can use these strategies have the best chance of successfully adjusting to the challenges posed by a chronic illness.

**PUBLIC HEALTH**


Rwanda is making substantial progress towards improvement of health and is working towards achievement of the Millennium Development Goals, which is a challenging task because the country has had genocide in 1994, has few natural resources, is landlocked, and has high population growth. Like many impoverished sub-Saharan countries, Rwanda’s health system has had an uncoordinated plethora of donors, shortage of health staff, inequity of access, and poor quality of care in health facilities. This report describes three health system developments introduced by the Rwandan government that are improving these barriers to care—ie, the coordination of donors and external aid with government policy, and monitoring the effectiveness of aid; a country-wide independent community health insurance scheme; and the introduction of a performance-based pay initiative. If these innovations are successful, they might be of interest to other sub-Saharan countries. However, Rwanda still does not have sufficient financial resources for health and will need additional external aid for some time to attain the Millennium Development Goals.


Symptomatic acute hepatitis C occurs in only about 15% of patients who are infected with hepatitis C virus (HCV). Acute hepatitis C is most often diagnosed in the setting of post-exposure surveillance, or seroconversion in high-risk individuals (eg, health-care professionals or injecting
drug users) previously known to be seronegative. Although transmission via transfusion and injecting drug use has declined in developed countries, unsafe blood products and medical practices continue to increase transmission of HCV in many developing countries. Clinically, acute hepatitis C can increase concentrations of alanine aminotransferase to ten times the upper limit of normal but almost never causes fulminant hepatic failure. Diagnosis of HCV infection in the acute phase is difficult since production of antibodies against HCV can be delayed by up to 12 weeks, and about a third of infected individuals might not have detectable antibody at the onset of symptoms. Therefore, testing for HCV RNA by PCR is the only reliable test for the diagnosis of acute infection. Symptomatic patients with jaundice have a higher likelihood of spontaneous viral clearance than do asymptomatic patients, and thus should be monitored for at least 12 weeks before initiating antiviral therapy. By contrast, asymptomatic patients have a much lower chance of spontaneous clearance, and might benefit from early antiviral therapy. Antiviral therapy for 12 weeks is generally effective in treating patients who are HCV RNA negative after 4 weeks of treatment; lengthier courses could be needed for those who relapse or fail to show early virological clearance.

HEALTH POLICY

John Guertin Gordon. (2008). A critique of the financial requirements to fight HIV/AIDS. The Lancet, 372 (9635), 333-336. Funds available for HIV/AIDS programmes in low-income and middle-income countries rose from US$300 million in 1996 to $10 billion in 2007. However, a combination of worldwide economic uncertainty, a global food crisis, and publications that indicate discontent with progress in fighting the HIV/AIDS pandemic will not only threaten to restrict increases in the overall availability of both donor and national funds, but will also increase the competition for resources during the move towards universal access to treatment and prevention services. Thus, UNAIDS will be under increasing pressure in its presentation and justification of resources needed for HIV/AIDS programming. Here I discuss UNAIDS’ 2007 estimates of resource requirements for fighting HIV/AIDS in terms of their usefulness to both donor and recipient governments for budget planning and for setting priorities for HIV/AIDS programmes. I identify weaknesses in the UNAIDS estimates in terms of financial transparency and priority setting, and recommend changes to improve budgeting and priority setting.