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"Thinking about health as the right of every citizen provides a framework for protecting and advancing the outcomes that the NHS seeks to achieve."

"A new oral drug: laquinimod at 0–6 mg daily, reduces new MRI lesions in relapsing-remitting multiple sclerosis."

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WORLD REPORTS

Doctors from a private hospital in Milan—dubbed the “clinic of horrors” by Italian press—have been arrested for doing unnecessary operations for financial gain and causing the deaths of patients. A 2-year police wiretap operation provided evidence for the case. Emma Baines reports. The arrest of 13 doctors from a private hospital in Italy on charges that range from fraud to murder has shaken confidence in the country’s healthcare system. Doctors working at Istituto Clinico Santa Rita in Milan are accused of having done unnecessary surgeries for financial gain. On June 9, 2008, the Milan branch of the Italian financial police arrested the doctors who have worked at Santa Rita over the past 2 years, together with the owner of the clinic. They were charged with falsifying clinical records and defrauding the Italian national health service of around 2.5 million.

Three of the doctors were also accused of voluntary homicide aggravated by cruelty, for doing unnecessary operations leading to the deaths of at least five patients. The Milan-based national paper Corriere della Sera published details of these unnecessary surgeries taken from a 200-page charge sheet.

Non-governmental organisations do life-saving work in developing nations but inadvertently their actions, fuelled by the pressure for quick results, can be detrimental to public-health systems. Can a new code of conduct, launched last month, help solve the problem? Nellie Bristol reports. International non-governmental organisations (NGOs) signed a code of conduct to help strengthen health systems on May 29, 2008, and pledged to pursue practices that bolster the public sector in the countries in which they operate. Launched in Washington, DC, the document is intended to provide a framework for good practice and discourage international groups from hiring health workers from struggling public-health systems in developing countries. The code, which has 25 signatories so far, was developed by six NGOs, including Physicians for Human Rights, African Medical and Research Foundation (AMREF), and Oxfam UK, and was coordinated by Health Alliance International based in Seattle, Washington.

The past 4 years has seen several legislative developments to tackle Europe’s growing obesity problem including food labelling, controls on junk-food advertising to children, and bans on fizzy drinks in school vending machines. But critics say they are not enough. Rob Hyde reports. Humble pie is not easy to swallow, but in early 2007, the European Union (EU) health commissioner Markos Kyprianous left no uncertainties about how Europeans had to digest the unpleasant truth—more than 50% of adults in Europe were obese or overweight. In the WHO European Region, three times more people are obese today than in the past 20 years, and a staggering ten times more children are obese than in the 1970s. In 2006, the EU announced that an estimated 7% of health costs were being spent treating cases of obesity. According to Erik Millstone, who heads the nine-country EU project—Policy Options for Responding to the Growing Challenge from Obesity (PorGrow)—many governments are so concerned about the effect of the epidemic of obesity on public expenditure, it is leading to calls for tough measures. “In the UK, for example, it is the Treasury, rather than the Department of Health, which is pushing hardest for obesity to be addressed, so that NHS [National Health Service] budgets can be used to help the . . .

Overseas aid for health is falling well short of what is needed to meet the Millennium Development Goals. A report out this week calls for Europe to fill the gap by not only donating more money but also by spending its current contributions more effectively. Karen McCull reports. The world urgently needs more aid for health that is better spent, if we are to reach the health-related Millennium Development Goals (MDGs). That is the message of a report released this week about how aid for health is donated from Europe. Policy makers have long known that the way aid is delivered needs to be improved for it to be fully effective. There are more than 40 bilateral donors, 26 UN agencies, 20 global and regional funds, and 90 global-health initiatives. In such a complex environment, donors clearly need to coordinate and harmonise their efforts, to ensure that external aid is in line with national priorities, and to focus on achieving and measuring real results. In 2005, a set of principles for better aid delivery were agreed in the Paris Declaration on Aid Effectiveness (see panel).

The number of suicides in Japan in 2007 is expected to exceed 30 for the 10th year in a row. The figure is proof that national efforts to tackle the problem are not working, say critics, who are urging the government to adopt better anti-suicide measures. Justin McCurry reports. Japan is to review its anti-suicide measures to adopt better anti-suicide measures. Justin McCurry reports. Japan is to review its anti-suicide measures after new estimates showed that it will fall a long way short of its target of cutting the country’s suicide rate by a fifth by 2016. Last year, Japan adopted a slew of measures designed to shake off its reputation as one of the world’s suicide hotspots, where one person takes their own life every 15 minutes on average. But, in a stunning admission of failure, the government’s chief spokesman, Nobutaka Machimura, said his “heart
achieved" ahead of the release of data that is expected to show that the number of Japanese who killed themselves last year exceeded 30 for the 10th year in a row. The rethink of suicide-prevention policies comes amid growing concern about suicides involving the inhalation of the deadly gas hydrogen sulphide, which can be produced by mixing shop-bought household detergents.


A debate is raging in North America over the safety of bisphenol A—a chemical found in a wide range of plastic products, including polycarbonate baby bottles. Canada is taking steps to limit infant exposure to the substance, while the USA says the chemical is safe. Paul Webster reports. The Canadian government says it aims to become the first government in the world to label bisphenol A—a chemical widely used in plastic food containers, medical devices, and several other products—toxic under a health-protection law later this year. Once that’s done, Canadian Health Minister Tony Clement says he will begin banning products containing bisphenol A. “I am proposing precautionary action to reduce exposure and increase safety”, Clement explains. “It is our intention to ban the importation, sale, and advertising of polycarbonate baby bottles. With this action, Canada will be the first country in the world to take such action to limit exposures to bisphenol A.”

**ARTICLES**

**Celum, C., Anna Wald, James Hughes, Jorge Sanchez, Steward Reid, Sinead Delany-MoretIwe, Frances Cowan, Martin Casapia, Abner Ortiz, Jonathan Fuchs, Susan Buchbinder, Beryl Koblin, Sheryl Zwerski, Scott Rose, Jing Wang, and Lawrence Corey. (2008).** Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet, 371* (9630), 2109-2119.

Across many observational studies, herpes simplex virus type 2 (HSV-2) infection is associated with two-fold to three-fold increased risk for HIV-1 infection. We investigated whether HSV-2 suppression with aciclovir would reduce the risk of HIV-1 acquisition. We undertook a double-blind, randomised, placebo-controlled phase III trial in HIV-negative, HSV-2 seropositive women in Africa and men who have sex with men (MSM) from sites in Peru and the USA. Participants were randomly assigned by block randomisation to twice daily aciclovir 400 mg (n=1637) or matching placebo (n=1640) for 12–18 months, and were seen monthly for dispensation of study drug, adherence counselling and measurement by pill count and self-reporting, and risk reduction counselling, and every 3 months for genital examination and HIV testing.

The primary outcome was HIV-1 acquisition and secondary was incidence of genital ulcers. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00076232. 3172 participants (1358 women, 1814 MSM) were included in the primary dataset (1581 in aciclovir group, 1591 in control group). The incidence of HIV-1 was 3·9 per 100 person-years in the aciclovir group (75 events in 1935 person-years of follow-up) and 3·3 per 100 person-years in the placebo group (64 events in 1969 person-years of follow-up; hazard ratio 1·16 [95% CI 0·83–1·62]). Incidence of genital ulcers on examination was reduced by 47% (relative risk 0·53 [0·46–0·62]) and HSV-2 positive genital ulcers by 63% (0·37 [0·31–0·45]) in the aciclovir group. Adherence to dispensed study drug was 94% in the aciclovir group and 94% in the placebo group, and 85% of expected doses in the aciclovir group and 86% in the placebo group. Retention was 85% at 18 months in both groups (1028 of 1212 in aciclovir group, 1030 of 1208 in placebo group). We recorded no serious events related to the study drug. Our results show that suppressive therapy with standard doses of aciclovir is not effective in reduction of HIV-1 acquisition in HSV-2 seropositive women and MSM. Novel strategies are needed to interrupt interactions between HSV-2 and HIV-1.


A 24-week phase II trial has shown that 0·3 mg of laquinimod given daily to patients with relapsing-remitting multiple sclerosis was well tolerated and reduced the formation of active lesions. We assessed the effect of oral daily 0·3 and 0·6 mg laquinimod on MRI-monitored disease activity in a 36-week double-blind, placebo-controlled phase IIb study. The study was done in 51 centres in nine countries. Inclusion criteria were one or more relapses in the year before entry and at least one gadolinium enhancing (GdE) lesion on screening MRI. Of 720 patients screened, 306 eligible patients were enrolled. Patients, aged 18–50 years, were randomly assigned to placebo (n=102), laquinimod 0·3 mg a day (n=98), or 0·6 mg a day (n=106). Brain MRI scans and clinical assessments were done at week -4, baseline, and monthly from week 12 to week 36. The primary outcome was the cumulative number of GdE lesions at weeks 24, 28, 32, and 36. The principal analysis of the primary endpoint was done on the intention-to-treat cohort. This study is registered with ClinicalTrials.gov, number NCT00349193. Compared with placebo, treatment with laquinimod 0·6 mg per day showed a 40-4% reduction of the baseline adjusted mean cumulative number of GdE lesions per scan on
the last four scans (simple means 4·2 [SD 9·2] vs 2·6 [5·3], p=0·0048); treatment with 0·3 mg per day showed no significant effects (3·9 [5·5] vs placebo, p=0·6740). Both doses of laquinimod were well tolerated, with some transient and dose-dependent increases in liver enzymes. A case of Budd-Chiari syndrome—ie, a thrombotic venous outflow obstruction of the liver—occurred after 1 month of exposure in a patient with underlying hypercoagulability who received 0·6 mg laquinimod. Anticoagulant treatment resulted in a decline of liver enzymes to normal without any clinical signs of hepatic decompensation. In patients with relapsing-remitting multiple sclerosis, 0·6 mg per day laquinimod significantly reduced MRI-measured disease activity and was well tolerated.


Sub-Saharan Africa has a high rate of HIV infection, most of which is attributable to heterosexual transmission. Few attempts have been made to assess the extent of HIV transmission within marriages, and HIV-prevention efforts remain focused on abstinence and non-marital sex. We aimed to estimate the proportion of heterosexual transmission of HIV which occurs within married or cohabiting couples in urban Zambia and Rwanda each year. We used population-based data from Demographic and Health Surveys (DHS) on heterosexual behaviour in Zambia in 2001–02 and in Rwanda in 2005. We also used data on the HIV serostatus of married or cohabiting couples and non-cohabiting couples that was collected through a voluntary counselling and testing service for urban couples in Lusaka, in Zambia, and Kigali, in Rwanda. We estimated the probability that an individual would acquire an incident HIV infection from a cohabiting or non-cohabiting sexual partner, and then the proportion of total heterosexual transmission which occurs within married or cohabiting couples in these settings each year. We analysed DHS data from 1739 Zambian women, 540 Zambian men, 1176 Rwandan women, and 606 Rwandan men. Under our base model, we estimated that 55-1% to 92-7% of new heterosexually acquired HIV infections among adults in urban Zambia and Rwanda occurred within serodiscordant marital or cohabiting relationships, depending on the sex of the index partner and on location. Under our extended model, which incorporated the higher rates of reported condom use that we found with non-cohabiting partners, we estimated that 60-3% to 94-2% of new heterosexually acquired infections occurred within marriage or cohabitation. We estimated that an intervention for couples which reduced transmission in serodiscordant urban cohabiting couples from 20% to 7% every year could avert 35·7% to 60·3% of heterosexually transmitted HIV infections that would otherwise occur. Since most heterosexual HIV transmission for both men and women in urban Zambia and Rwanda takes place within marriage or cohabitation, voluntary counselling and testing for couples should be promoted, as should other evidence-based interventions that target heterosexual couples. US National Institute of Mental Health, National Institute of Child Health and Human Development, National Institute of Allergy and Infectious Diseases. Fogarty AIDS International Training and Research Program, Emory Center for AIDS Research, and the International AIDS Vaccine Initiative.


Treatments for pulmonary arterial hypertension have been mainly studied in patients with advanced disease (WHO functional class [FC] III and IV). This study was designed to assess the effect of the dual endothelin receptor antagonist bosentan in patients with WHO FC II pulmonary arterial hypertension. Patients with WHO FC II pulmonary arterial hypertension aged 12 years or over with 6-min walk distance of less than 80% of the normal predicted value or less than 500 m associated with a Borg dyspnoea index of 2 or greater were enrolled in this double-blind, placebo-controlled, multicentre trial. 185 patients were randomly assigned to receive bosentan (n=93) or placebo (n=92) for the 6-month double-blind treatment period via a centralised integrated voice recognition system. Primary endpoints were pulmonary vascular resistance at month 6 expressed as percentage of baseline and change from baseline to month 6 in 6-min walk distance. Analyses of the primary endpoints were done with all randomised patients who had a valid baseline assessment and an assessment or an imputed value for month 6. This trial was registered with ClinicalTrials.gov, number NCT00091715. Analyses were done with 168 patients (80 in the bosentan group, 88 in the placebo group) for pulmonary vascular resistance and with 177 (86 and 91) for 6-min walking distance. At month 6, geometric mean pulmonary vascular resistance was 83-2% (95% CI 73-8–93-7) of the baseline value in the bosentan group and 107-5% (97-6–118-4) of the baseline value in the placebo group (treatment effect -22-6%, 95% CI -33-5 to -10-0; p<0·0001). Mean 6-min walk distance increased from baseline in the bosentan group (11-2 m, 95% CI -4-6 to 27-0) and decreased in the placebo group (-7·9 m, 24-3 to 8-5), with a mean treatment effect of 19-1 m (95% CI 3-6–41-8; p=0·0758). 12 (13%) patients in the bosentan group and eight (9%) in the placebo group reported serious adverse events, the most common of which were syncope in the bosentan group.
and right ventricular failure in the placebo group. Bosentan treatment could be beneficial for patients with WHO FC II pulmonary arterial hypertension.


Axitinib (AG-013736) is a potent and selective oral inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, which have an important role in pancreatic cancer. The aim of this study was to assess the safety and efficacy of gemcitabine plus axitinib versus gemcitabine alone. Between January and August, 2006, 103 patients with unresectable, locally advanced, or metastatic pancreatic cancer were randomly assigned in a two to one ratio to receive gemcitabine (1000 mg/m²) alone (n=69) or gemcitabine (1000 mg/m²) plus axitinib 5 mg twice daily (n=34) by a centralised registration system. The primary endpoint was overall survival. Analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00219557. All randomised patients were included in the efficacy analyses. Median overall survival was longer with gemcitabine plus axitinib than with gemcitabine alone (6-9 [95% CI 5·3–10·1] months vs 5·6 [3·9–8·8] months). The hazard ratio for survival with gemcitabine plus axitinib versus with gemcitabine alone, adjusted for stratification factors, was 0·71 (95% CI 0·44–1·13). The most common grade 3 or worse adverse events were fatigue (15 [22%] patients in the gemcitabine plus axitinib group vs one [3%] in the gemcitabine alone group), abdominal pain (eight [12%] vs five [16%]), and asthenia (eight [12%] vs one [3%]). Gemcitabine plus axitinib showed a similar safety profile to gemcitabine alone; the small, non-statistically significant gain in overall survival needs to be assessed in a randomised phase III trial.

**Wen, CP., Ting Yuan Cheng, Min Kuang Tsai, Yen Chen Chang, Hui Ting Yuan, Shan Pou Tsai, Po Huang Chiang, and Chih Cheng Hsu. (2008). All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 4620293 adults in Taiwan. Lancet, 371 (9631), 2173-2182.**

Both end-stage renal disease and chronic kidney disease are increasing worldwide; however, the full effect of chronic kidney disease is unknown because mortality risks for all five stages are unavailable. We assessed prevalence and mortality risks for all stages of chronic kidney disease and quantified its attributable mortality in Taiwan. The cohort consisted of 4620293 individuals aged older than 20 years who participated in a standard medical screening programme since 1994. As of Dec 31, 2006, we identified 140436 deaths. Chronic kidney disease was determined by glomerular filtration rate and urinary protein. We estimated national prevalence in Taiwan from the cohort by adjusting age and educational levels. Hazard ratios (HRs) were calculated with Cox proportionate hazards model. We calculated mortality attributable to chronic kidney disease for national population and for low socioeconomic status. The national prevalence of chronic kidney disease was 11·93% (95% CI 11·66–12·28), but only 3·54% (3·37–3·68) of participants in the cohort were aware of their disorder. Prevalence was substantially higher in the group with low socioeconomic status than in the high status group (19·87% [19·84–19·91] vs 7·33% [7·31–7·35]). 567977 (12%) of cohort participants had chronic kidney disease; those with disease had 83% higher mortality for all cause (HR 1·83 [1·73–1·93]) and 100% higher for cardiovascular diseases (2·00 [1·78–2·25]), in a cohort that was observed for 13 years with median follow-up of 7·5 years (IQR 4·0–10·1). 10·3% (95% CI 9·57–11·03) of deaths in the entire population were attributable to chronic kidney disease, but 17·5% (16·27–18·67) of deaths in the low socioeconomic status population. 2350 (39%) deaths occurred before 65 years of age in those with chronic kidney disease. Regular users of Chinese herbal medicines had a 20% (odds ratio 1·20 [1·16–1·24]) increased risk of developing chronic kidney disease. The high prevalence of chronic kidney disease and its associated all-cause mortality, especially in people with low socioeconomic status, make reduction of this disorder a public-health priority.

**SEMINAR**


Spinal muscular atrophy is an autosomal recessive neurodegenerative disease characterised by degeneration of spinal cord motor neurons, atrophy of skeletal muscles, and generalised weakness. It is caused by homozygous disruption of the survival motor neuron 1 (SMN1) gene by deletion, conversion, or mutation. Although no medical treatment is available, investigations have elucidated possible mechanisms underlying the molecular pathogenesis of the disease. Treatment strategies have been developed to use the unique genomic structure of the SMN1 gene region. Several candidate treatment agents have been identified and are in various stages of development. These and other advances in medical technology have changed the standard of care for patients with spinal muscular atrophy. In this Seminar, we provide a comprehensive review that integrates clinical manifestations, molecular pathogenesis, diagnostic strategy, therapeutic development, and evidence from clinical trials.
Restenosis is a serious occurrence that can lead not only to recurrent angina and repeat revascularisation but also to acute coronary syndromes. Drug-eluting stents revolutionised interventional cardiology owing to their pronounced ability to reduce restenosis compared with bare-metal stents. Attention has now shifted to safety of these devices because of evidence suggesting an association with late stent thrombosis. Findings of randomised clinical trials have not shown that drug-eluting stents result in excess mortality after 4–5 years of follow-up. Current recommendations are that individuals with a drug-eluting stent should receive at least 12 months of uninterrupted dual antiplatelet treatment; patients must understand the importance of this long-term regimen. Patients’ assessment should focus on bleeding abnormalities, pre-existing disorders that need anticoagulation treatment, and possible future surgical procedures, since these factors could all contraindicate use of drug-eluting stents. Many people will do well with a bare-metal stent, whereas for individuals with a high likelihood of restenosis and late thrombosis, medical management or surgical revascularisation might be preferred options.