General

Coffee drinking and reduced mortality

Although coffee drinking has been regarded with suspicion because of the stimulant properties of caffeine there is accumulating evidence that drinking coffee may be associated with health benefits. Now a large US cohort study has shown an inverse relationship between coffee drinking and mortality.

The National Institute of Health-AARP Diet and Health Study included 229 119 men and 173 141 women aged 50–71 and free of cancer, heart disease, or stroke history at baseline in 1995–1996. Between 1995 and 2008, 33 731 men and 18 784 women died. Before adjustment, mortality was increased among coffee drinkers but after adjustment for smoking and other possible confounders coffee drinking was associated with reduced mortality. Among men there were significant reductions in overall mortality of 6% with one cup of coffee a day, 10% (two or three cups), 12% (four or five cups), and 10% (six or more cups). Among women there was a nonsignificant reduction of 5% with one cup a day, and significant reductions of 13% (two or three cups), 16% (four or five cups), and 15% (six or more cups). The inverse association applied to deaths from heart disease, respiratory disease, stroke, injury, diabetes, and infections, but not from cancer. The results were similar in subgroups including lifetime non-smokers and healthy people and in drinkers of caffeinated and decaffeinated coffee.

Coffee drinking was associated with reduced mortality. Whether the association is causal is not known.

Freedman ND et al. Association of coffee-drinking with total and cause-specific mortality. *NEJM* 2012; 366: 1891–904.

Noncommunicable disease risk factors in prisons worldwide

A systematic review has focussed on the prevalence of poor diet, inadequate physical activity, and overweight and obesity in prisoners worldwide.

The review included 31 studies with more than 60 000 prisoners in 884 institutions in 15 countries. In all but one study the prevalence of obesity in men prisoners was less than in the general population, but female prisoners were more likely to be obese than women in the general population in the USA and Australia. Prisoners in Australia had more exercise than the general population but prisoners in the UK had less. Energy intake was high for female prisoners and for all prisoners salt intake was two or three times that recommended.

Health promotion in prisoners needs to be improved.

Herbert K et al. Prevalence of risk factors for non-communicable disease in prison populations worldwide: a systematic review. *Lancet* 2012; 379: 1975–82; Arnold FW. Non-communicable diseases in prisons. Ibid: 1931–3 (comment).

Vitamin D dosage to prevent fractures: pooled analysis of 11 trials

Most fractures occur in the elderly and the global incidence of fractures is expected to increase considerably in the next few decades. Meta-analyses of trials of vitamin D to prevent fractures have given varying results. A pooled analysis of individual participant data from 11 trials has aimed to assess the dose of oral vitamin D necessary to prevent fractures.

The trials included 31 022 people (mean age 76, 91% women) with 1111 first hip fractures and 3770 nonvertebral fractures. Overall, subjects assigned to vitamin D had a nonsignificant 10% reduction in risk of hip fracture compared with controls. There was a nonsignificant 7% reduction in risk of nonvertebral fractures. Only in the highest quartile of actual vitamin D intake (median intake 800 IU daily, range 792–1000 IU) were there significant reductions in risk of hip fracture (by 30%) and any nonvertebral fracture (by 14%). Subgroups defined by age group, type of dwelling, baseline 25-hydroyvitamin D level, and additional calcium intake benefitted similarly at the highest vitamin D intake level.

Among people aged 65 or older, high doses of oral vitamin D (800 IU a day or more) were effective in preventing hip fracture or any nonvertebral fracture. Possible toxicity was not addressed in this analysis.

Bischoff-Ferrari HA et al. A pooled analysis of vitamin D dose requirements for fracture prevention. *NEJM* 2012; 367: 40–9.

Cardiology

Heart failure – warfarin or aspirin

Heart failure may be associated with hypercoagulability. Studies of anticoagulant therapy have given varying results. Now a multinational trial has shown no difference in outcomes with aspirin or warfarin treatment.

A total of 2305 patients (mean age 61 years, 80% men) with sinus rhythm and a reduced left ventricular ejection fraction (35% or less) were randomised at 168 centres in 11 countries to warfarin (target INR 2.0–3.5) or aspirin 325 mg a day. Follow-up was up to 6 years. The primary outcome (ischaemic stroke, intracerebral haemorrhage, or death from any cause) occurred at a rate of 7.47 events per 100 patient–years in the warfarin group and 7.93 events per 100 patient–years in the aspirin group, a nonsignificant difference. There was a trend towards better results with warfarin over the long term. There was a significant reduction in the rate of ischaemic stroke with warfarin compared with aspirin (0.72 vs 1.36 events per 100 patient–years) but a greater risk of major haemorrhage with warfarin (1.78 vs 0.87 events per 100 patient–years. The rates of intracerebral and intracranial haemorrhage were similar in the two groups.

The overall results were similar in the two groups. Compared with aspirin, warfarin was associated with less risk of ischaemic stroke but greater risk of major haemorrhage. It is concluded that there is no compelling reason to use warfarin rather than aspirin for these patients.

Homma S et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. *NEJM* 2012; 366: 1859–69; Eikelboom JW, Connolly SJ. Warfarin in heart failure. Ibid: 1936–8 (editorial).

Cardiovascular protection from dark chocolate

Consumption of dark chocolate has been shown to have cardiovascular benefits by reducing systolic blood pressure and lipid levels. Use of a Markov model with patients with the metabolic syndrome but not diabetes, and without known cardiovascular disease at baseline, in the Australian *Diabetes Obesity and Lifestyle* study has provided an assessment of the benefits. Among these patients, dark chocolate consumption over a period of 10 years could potentially prevent 70 nonfatal cardiovascular events and 15 fatal cardiovascular events per 10 000 population. At a spending on dark chocolate of up to £25 (US$42) per person per year consumption of dark chocolate would be cost-effective.

Eating dark chocolate could be cost-effective in preventing cases of cardiovascular disease in patients with the metabolic syndrome.

Zomer e et al. The effectiveness and cost effectiveness of dark chocolate consumption as a prevention therapy in people at high risk of cardiovascular disease: best case scenario analysis using a Markov model. *BMJ* 2012; 344 (June 23) 18 (e3657).

Hormonal contraception and cardiovascular risk

A Danish registry study has provided more data about cardiovascular risks associated with hormonal contraception.

Data were obtained from four national registries over a 15-year period about non-pregnant women aged 15–49 with no history of cardiovascular disease or cancer. The data included 1 626 158 women with 14 251 063 person–years of observation, during which there were 3311 thrombotic strokes and 1725 myocardial infarctions. The rate of thrombotic stroke was 21.4 per 100 000 person–years and of myocardial infarction, 10.1 per 100 000 person–years. Among women using oral contraceptives including ethinyl oestradiol at a dose of 30–40 µg the risk of thrombotic stroke was increased 1.5 to 2.2-fold according to progestin type, compared with non-users. The risk of myocardial infarction was increased 1.3 to 2.3-fold. At an ethinyl oestradiol dose of 20 µg the increase in risk was less in general and there was no increased risk with drospirenone as the progestin. Transdermal patches were not associated with significantly increased risk for either thrombotic stroke or myocardial infarction. Vaginal ring was associated with a significant 2.5-fold increase in risk of thrombotic stroke but a nonsignificant increase in risk of myocardial infarction.

Although hormonal contraception may increase the risks of thrombotic stroke and myocardial infarction the absolute risks are low. An editorialist concludes that they are 'safe enough'.

Lidegaard Ø et al. Thrombotic stroke and myocardial infarction with hormonal contraception. *NEJM* 2012; 366: 2257–66; Petitti DB. Hormonal contraceptives and arterial thrombosis – not risk-free but safe enough. Ibid: 2316–8 (editorial).

Paediatrics

Child mortality 2010

Many countries are not on track to reach Millennium Development Goal 4 (MDG4), a two-thirds reduction in mortality in children under the age of 5 years between 1990 and 2015. Statistics for 2010 have been reported.

In 2010, the global mortality among children under the age of 5 was 7.6 million children. Between 2000 and 2010 under-5s mortality fell from 73 to 57 deaths per 1000 live births. Of the 7.6 million deaths in 2010, 64% were from infections and 40.3% were in neonates. The main causes of neonatal death were complications of preterm birth (14.1%), intrapartum-related complications (9.4%), and sepsis or meningitis (5.2%). Among children aged 1-59 months the main causes were pneumonia (14.1%), diarrhoea (9.9%), and malaria (7.4%). Between 2000 and 2010 global deaths of children <5 years old were reduced by 2 million, the reduction being largely due to fewer deaths from pneumonia, measles, and diarrhoea. Reduction rates consistent with MDG4 were achieved only for tetanus, measles, AIDS, and malaria (in Africa)

Effects to reduce child mortality should concentrate on infectious diseases and neonatal mortality.

Liu L et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet* 2012; 379: 2151–61; Bhutta ZA. Global child survival: beyond numbers. Ibid: 2126–8 (comment).

Preterm births worldwide

Among children <5 years old, preterm birth is the second largest cause of death but data about preterm births are not collected routinely. Available data for 184 countries for 2010 have been reported.

It is estimated that in 2010 some 14.9 million babies were born preterm (before 37 completed weeks of gestation). The rate ranged from 5% in some European countries to 18% in some African countries. More than 60% of all preterm births were in south Asia and sub-Saharan Africa, where 52% of live births occur. The USA had a high rate of preterm birth, being ranked sixth for total number (517 443) with a rate of 12% of live births. Among 65 countries with time trend data only Croatia, Ecuador, and Estonia had a reduction in preterm birth rates between 2000 and 2010.

The rate of preterm birth is increasing in many countries. Better data are needed.

Blencowe H et al. National, regional, and worldwide estimate of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012; 379: 2162–72; Morken N-H. Preterm birth: new data on a global health priority. Ibid: 2128–30 (comment).

Reducing measles mortality

One global goal was to halve measles deaths between 1999 and 2005 and that was achieved. A new goal was then set, to reduce measles mortality by 90% between 2000 and 2010. There has been no endemic measles virus transmission in the Americas since 2002 and only the southeast Asia region of the World Health Organization (WHO) has not set an aim of measles elimination by 2020. Measles mortality fell by an estimated 74% between 2000 and 2010, from 535 300 to 139 300 deaths. All regions except southeast Asia achieved a reduction of >75%. In India, measles deaths fell by 25% from 88 000 to 65 500. In 2010, almost half (47%) of all deaths from measles were in India and 56% were in Africa. Achievement of the 2000–2010 goal was impeded by delayed implementation of disease control in India and outbreaks of measles in Africa. Greater political and financial commitment are needed.

Simons E et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. *Lancet* 2012; 379: 2173–8; Orenstein WA, Hinman AR. Measles: the burden of preventable deaths. Ibid: 2130–1 (comment).

The Millennium Villages project in Africa

The Millennium Villages project began in nine African countries (Nigeria, Mali, Senegal, Ghana, Uganda, Kenya, Rwanda, Tanzania, and Malawi) in 2006. In each country a rural population (average 35 000 people) with high levels of poverty and undernutrition was selected. Finance amounting to around US$120 per person was provided annually to support agriculture, the environment, business development, education, infrastructure, and health, in partnership with communities and local governments. Average spending per person was $27 at baseline and $116 by year 3. There were improvements in water supplies and sanitation, poverty levels, food security, stunting, and malaria prevalence at Millennium Village sites after 3 years. Under-5s mortality fell by 22% in these sites and by 33% relative to matched comparison sites. Provision of many maternal–child health interventions was improved.

The multifaceted intervention was beneficial in several ways including reduced child mortality.

Pronyk PM et al. The effect of an integrated multisector model for achieving the Millennium Development Goals and improving child survival in rural sub-Saharan Africa: a non-randomised controlled assessment. *Lancet* 2012; 379: 2179–88; Malenga G, Molyneux M. The Millennium Villages project. Ibid: 2131–3.

Obs & Gyn

Elective induction of labour at term

The merits of elective induction of labour at term have long been debated. A study in Scotland has suggested that elective induction might reduce perinatal mortality but increase admissions to the neo-

natal unit.

The retrospective cohort study included 1 271 549 singleton births at >36 completed weeks in which there was no contraindication to induction of labour. At gestations between 37 and 41 completed weeks elective induction of labour was associated with reduced perinatal mortality compared with expectant management. At 40 weeks the reduction was from 1.8 to 0.8 per 1000, a significant 61% reduction after adjustment for maternal age, parity, year of birth, birth weight, deprivation, and mode of delivery. The odds of spontaneous vertex delivery were increased significantly by 26% after induction of labour. The rate of admission to the neonatal unit was increased significantly by 14%. Elective induction of labour at 40 weeks would prevent one neonatal death in 1040 deliveries and result in seven extra admissions to the neonatal unit.

Elective induction of labour at term would reduce perinatal mortality without increasing the rate of operative delivery but with an increase in neonatal unit admissions.

Stock SJ et al. Outcomes of elective induction of labour compared with expectant management: population based study. *BMJ* 2012; 344: 19 (e2838).

Dietary and lifestyle interventions in pregnancy

A meta-analysis has shown that dietary intervention in pregnancy can reduce maternal weight gain without increasing rates of smallness-for-gestational age in infants.

The meta-analysis included 44 randomised trials (7278 women). For all interventions there was an average 1.42 kg reduction in weight gain in pregnancy compared with controls. Dietary interventions produced an average reduction in weight gain of 3.84 kg without significant reduction in birth weight. The incidence of large- or small-for-gestational age infants was not affected. Interventions were associated with significant reductions in risk of pre-eclampsia (by 26%) and shoulder dystocia (by 61%). Dietary intervention was associated with the largest gain. Increased physical activity was associated with reduced birth weight.

Dietary intervention in pregnancy may reduce maternal weight gain and improve obstetric outcomes.

Thangaratinam S et al. Effects f interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. *BMJ 2012; 449 (May 26): 14 (e2088): Poston L,* Chappell LC. How should women be advised on weight management in pregnancy? Ibid: 8 (e2774) (editorial).

Infection

Drotrecogin alfa (activated) in septic shock: no reduction in mortality

After a study reported in 2001, recombinant human activated protein C (drotrecogin alfa (activated) or Drot AA) was approved for the treatment of severe sepsis. That study had shown a 6.1 percentage point reduction in mortality (a 19.4% absolute reduction). The benefit appeared to be restricted to severely ill patients. Subsequent trials on less severely ill adults and children were terminated early because of futility. In 2007 a new trial was considered warranted and that trial has now been reported.

The multinational trial included 1696 adults with infection, systemic inflammation, and shock (on fluids and vasopressors) with randomisation to Drot AA or placebo for 96 hours. At 28 days, mortality was 26.4% (Drot AA) vs 24.2% (placebo), a nonsignificant difference. At 90 days, mortality was 34.1% vs 32.7%. Among patients with severe protein C deficiency at baseline, 28-day mortality was 28.7% vs 30.8%. The rate of serious bleeding during treatment was similar in the two groups (10 patients vs 8).

Drot AA did not reduce mortality in patients with septic shock.

Ranieri VM et al. Drotrecogin alfa (activated) in adults with septic shock. *NEJM* 2012; 366: 2055–64; Wenzel RP, Edmond MB. Septic shock-evaluating another failed treatment. Ibid: 2122–4 (editorial).

Delamanid for multidrug-resistant pulmonary tuberculosis

Worldwide, about 5% of cases of tuberculosis are multidrug-resistant. Such cases are difficult to treat, requiring combinations of up to six drugs and with lower cure rates than with drug-susceptible tuberculosis. Delamanid (OPC-6783) is a new antituberculous drug, a nitrodihydro-imadooxazole derivative that inhibits mycobacterial synthesis of mycolic acid and is active against drug resistant strains of Mycobacterium tuberculosis in vitro and in vivo. A multicentre trial in nine countries has shown that delamanid is effective in multidrug-resistant pulmonary tuberculosis.

A total of 481 HIV-negative patients with multidrug-resistant pulmonary tuberculosis were given a background drug regimen and randomised in addition to delamanid 100 mg twice daily, delamanid 200 mg twice daily, or placebo. Sputum-culture conversion in liquid broth at 2 months was achieved in 45% (100 mg dose), 41.9% (200 mg dose), and 29.6% (placebo), a significant improvement on placebo for both doses of delamanid. Most adverse events were of mild or moderate severity and occurred at similar rates in the three groups. Delamanid was significantly associated with prolongation of the QT interval on ECG but there were no clinical events associated with this finding.

Delamanid increased the rate of sputum-culture conversion at 2 months in patients with multidrug-resistant pulmonary tuberculosis.

Gler MT et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *NEJM* 2012; 366: 2151–60; Chaisson RE, Nuermberger EL. Confronting multidrug-resistant tuberculosis. Ibid: 2223–4 (editorial).

AIDS

Treatment for infants of mothers who present late in pregnancy with an untreated HIV-1 infection

The best treatment for infants of mothers with HIV-1 infection who have not received antiretroviral therapy (ART) in pregnancy is uncertain. Three regimens have been compared in an international trail.

A total of 1684 bottle-fed infants of mothers who received a diagnosis of HIV-1 infection late in pregnancy were randomised within 48 hours of birth in Brazil, South Africa, Argentina, or the USA to one of three treatment regimens: zidovudine for 6 weeks (Z6), zidovudine for 6 weeks plus three doses of nevirapine in the first 8 days (Z6 + Nev), or zidovudine for 6 weeks plus nelfinavir and lamivudine for 2 weeks (Z6 + Nelf L). The overall rate of in utero HIV- transmission was 5.7% and was the same in all three groups. Transmission during labour occurred in 4.8% (Z6), 2.2% (Z6 + Nev), and 2.4% (Z6 + Nelf L). Overall, 8.5% of infants were infected by 3 months, 11.0% in the Z6 group, 7.1% in the Z6 + Nev group, and 7.4% in the Z6+Nelf L group, a significantly greater rate in the zidovudine-only group compared with the other two groups. HIV-1 transmission was significantly associated with zidovudine monotherapy, higher maternal HIV load, and maternal use of illegal substances. Neutropenia occurred in 16.4%, 14.9%, and 27.5% of the three groups respectively.

The Z6 + Nev and Z6+ Nelf L regimens were more effective than the Z6 regimen and the Z6+Nev was less toxic

than Z6 + Nef L.

Nielsen-Saines K et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *NEJM* 2012; 366: 2368–79.

Zidovudine, lamivudine, and ritonavir-boosted lopinavir for HIV-infected children

For mothers and infants who have previously been exposed to nevirapine treatment of HIV-1 infection with a regimen including ritonavir-boosted lopinavir is better than treatment with a nevirapine-based combination. The best treatment for children not previously exposed to nevirapine is uncertain. Now a trial in six countries in sub-Saharan Africa and India has shown that a ritonavir-boosted lopinavir-based regimen is better than a nevirapine-based regimen for young children who are nevirapine-naive.

A total of 287 nevirapine-naive HIV-infected children aged 2–36 months were randomised to zidovudine and lamivudine with either nevirapine or ritonavir-boosted lopinavir. The median proportion of CD4+T cells was 15% and median plasma HIV-1 RNA level 5.7 log10 copies per ml. Virological failure or treatment discontinuation by week 24 occurred in significantly more children in the nevirapine group (40.8% vs 19.3%). Drug resistance was present in 19 of 32 children in the nevirapine group tested at the time of virological failure. Mortality was greater in the nevirapine group (10/147 vs 3/140) and drug toxicity was also greater.

The results were better with the ritonavir-boosted lopinavir-based regimen but these researchers point to difficulties in introducing this treatment: the liquid formulation is unpleasant to taste and deteriorates in hot temperatures and the cost is twice that of the nevirapine-based regimen. New drug formulations are needed urgently.

Violari A et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *NEJM* 2012; 366: 2380–9.

Four-drug single tablet for initial treatment of HIV-1 infection

A single tablet to be taken once daily and containing four antiretroviral drugs has been developed. The four drugs are elvitegravir (an HIV integrase strand transfer inhibitor), cobicistat (a cytochrome P450 3A inhibitor with no antiretroviral activity that acts as a pharmacoenhancer), emtricitabine, and tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF). This combination has been compared with each of two standard regimens in successive papers in the *Lancet*.

A trial in Australia, Europe, North America, and Thailand included 708 patients with previously untreated HIV-1 infection (HIV-1 RNA 5000 copies per ml or more) susceptible to atazanavir, emtricitabine, and tenofovir. Randomisaiton was to EVG/COBI/FTC/TDF or ritonavir-boosted atazanavir plus emtricitabine, plus tenofovir (ATV/RTV+FTC/TDF, once daily. EVG/COBI/FTC/TDF was non-inferior to ATV/RTV+FTC/TDF with 89.5% vs 86.8% achieving the primary outcome of an HIV RNA level of 50 copies per ml or less after 48 weeks. Treatment discontinuation because of adverse events occurred in 3.7% vs 5.1%.

A multicentre trial in North America included 700 patients. Randomisation was to EVG/COBI/ FTC/TDF or efavirenz co-formulated with emtricitabine and tenofovir disoproxil fumarate (EFV/FTC/TDF). An HIV RNA concentration of <50 copies per ml at week 48 was achieved by 87.6% (EVG/COBI/FTC/TDF) vs 84.1% (EFV/FTC/TDF), showing non-inferiority of EVG/COBI/FTC/TDF. The rate of discontinuation because of adverse events was similar in the two groups. EVG/COBI/FTC/TDF caused more nausea and EFV/FTC/TDF caused more dizziness, abnormal dreams, insomnia, and rash.

It is concluded that, given regulatory approval, EVG/ COB/FTC/TDF would be the first once daily, single tablet, integrase-inhibitor-based regimen for initial HIV treatment.

Dejesus E et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet* 2012; 379: 2429–38; Sax PE et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Ibid: 2439–48; Schrijvers R, Debyser Z. Quad's in it for antiretroviral therapy? Ibid: 2403–5 (comment).

Preventing postnatal mother-to-infant HIV-1 transmission in Malawi

In many developing countries breastfeeding is essential for the infant but carries a risk of mother-to-infant-transmission of HIV. The Breastfeeding, Antiretroviral, and Nutrition (BAN) study in Malawi was first reported in 2010 and showed that 28 weeks of triple antiretroviral therapy to the mothers or of nevirapine to the infant significantly reduced the risk of HIV transmission to the infant during breastfeeding. Now the 48-week follow-up of that trial has been reported.

The trial included 2369 HIV-infected, breastfeeding mothers with a CD4 count of at least 250 cells per µL. Randomisation was to 28 weeks of maternal triple antiretroviral therapy, 28 weeks of daily nevirapine to the infant, or a control group. All mothers and infants received a single dose of nevirapine and 7 days of twice daily zidovudine and lamivudine. A total of 1898 mother-infant pairs completed 48 weeks of follow-up or reached an endpoint. Mothers were advised to wean their infants at 24–28 weeks and most had done so at 32 weeks. The rate of infant HIV infection between 2 weeks and 48 weeks of age was 30/676 (4.4%) in the maternal antiretrovirals group, 25/680 (3.7%) in the infant nevirapine group, and 38/542 (7.0%) in the control group. Twenty-eight (30%) of the infections occurred after 28 weeks. The risk of infant HIV infection by 48 weeks was significantly lower in each of the treatment groups compared with the control group. After 28 weeks, when maternal or infant treatment was stopped, the risk of diarrhoea, malaria, growth slowing, tuberculosis, or death in the infant increased significantly.

Antiretroviral prophylaxis to breastfeeding mothers or their infants is effective. Weaning at 6 months could increase morbidity in the infants. WHO now recommends antiretroviral prophylaxis to mothers or infants during 12 months of breastfeeding.

Jamieson DJ et al. Maternal and infant antiretroviral regimens to prevent postnatal HIV-1 transmission: 48-week follow-up of the BAN randomised controlled trial. *Lancet* 2012; 379: 2449–58; Kuhn L, Coovadia HM. Protecting infants of HIV-positive mothers in Malawi. Ibid: 2405–7 (comment).

Diabetes

Type 2 diabetes: exenatide or glimepiride as addition to metformin

There is uncertainty about the best additional treatment when glycaemic control with metformin is inadequate in type 2 diabetes. A trial in 14 countries has compared exenatide (a glucagon-like peptide-1 receptor agonist) with glimepiride (a sulphonylurea).

A total of 1029 patients with type 2 diabetes inadequately controlled on metformin were randomised to take in addition exenatide twice daily or glimepiride once daily. Treatment failure occurred in 41% (exenatide) vs 54% (glimepiride), a significant difference. An HbA_{1c} level of <7% was achieved by 44% vs 31%. There was an average loss of 3.32 kg of

bodyweight with exenatide and a gain of 1.15§kg on glimepiride. Hypoglycaemia was significantly less frequent with exenatide (36% vs 67%) but more patients in the exenatide group discontinued treatment within 6 months because of adverse events (mainly gastrointestinal).

Exenatide was more effective than glimepiride in this trial.

Gallwitz B et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. *Lancet* 2012; 379: 2270–8; Madsbad S. Type 2 diabetes: which drug as add-on to metformin? Ibid: 2222–3 (comment).

Pioglitazone and bladder cancer

Animal studies and observational studies in patients have suggested that pioglitazone might increase the risk of bladder cancer. Now a study using the UK general practice research database has provided further evidence.

The study included a cohort of 115 727 people with type 2 diabetes newly treated with oral antidiabetic drugs in 1988–2009. Average follow-up was for 4.6 years. There were 376 cases of bladder cancer and 6699 controls in the case-control study. Any use of pioglitazone significantly increased the risk of bladder cancer by 83% compared with never use of any thiozolidinedione. The risk increased with duration of use and cumulative dose, reaching a 99% increase after >24 months of use and a 2.54-fold increase with a cumulative dose of >28 g. No associations were observed with rosiglitazone use.

Pioglitazone is associated with increased risk of bladder cancer and doctors should consider whether its risk-benefit ratio is still acceptable.

Azoulay L et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *BMJ* 2012; 344 (June 23) 15 (e3645); Hillaire-Buys D, Faillie J-L. Pioglitazone and the risk of bladder cancer. Ibid: 7 (e3500).

Surgery

Tranexamic acid and surgical bleeding

Tranexamic acid may reduce bleeding during surgery but whether it promotes thromboembolism is not known. A systematic review and meta-analysis has included 95 randomised controlled trials.

Overall, use of tranexamic acid reduced the probability of blood transfusion significantly by 68%. The effects on myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism were not significant. There was a 39% reduction in risk of death with tranexamic acid but this was no longer significant when only trials with adequate concealment were analysed.

Tranexamic acid reduces the need for blood transfusion in surgery but more data are needed to assess its effect on thromboembolic events and mortality.

Ker K et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012; 344 (May 26): 15 (d5701)

Acute appendicitis: surgery versus antibiotics

Although surgery has been standard treatment for acute appendicitis for over 120 years there has been recent interest in treating uncomplicated acute appendicitis with antibiotics alone. A meta-analysis has supported the use of antibiotics without surgery.

The meta-analysis included four randomised controlled trials (900 adult patients) with randomisation to appendicectomy or antibiotic treatment for uncomplicated acute appendicitis. Patients were reviewed twice daily after admission and followed up for 1 year. The appendicectomy groups had open or laparoscopic appendicectomy with amoxicillin and clavulanic acid given at induction of anaesthesia. The antibiotic group were given i.v. or oral amoxicillin plus clavulanic acid for 48 hours. If symptoms has resolved they were discharged to take the antibiotic for another 8 days. If symptoms had not resolved after 48 hours or symptoms persisted at day 15, appendicectomy was performed. In the antibiotic group 68% of patients recovered without surgery. Readmission was necessary for 68 patients (20%). Three of these were treated successfully with another course of antibiotics and 65 underwent surgery: four had a normal appendix and 13 had complicated appendicitis. There was a significant 31% reduction in risk of complications in the antibiotic group compared with the appendicectomy group. Treatment efficacy, duration of hospital stay, and risk of complicated appendicitis were similar in the two groups.

It is concluded that antibiotic treatment (with surgery if necessary) is effective and safe for patients with uncomplicated acute appendicitis. An editorialist considers the issue unsettled.

Vardhan KK et al. Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trial. *BMJ* 2012; 344 (May 5): 14 (e2156); Bakker O. Should conservative treatment of appendicitis be first line? Ibid: 8 (e2546).

Psychology

Physical activity for depression: not effective

Studies have suggested that physical activity may be effective in relieving depression. Now a general practice study in England has shown no benefit.

A total of 361 patients aged 18–69 years with depression diagnosed by clinical interview schedule-revised and Beck depression inventory score were randomised to usual care plus facilitated physical activity or usual care alone. At 4 months there was no significant improvement in depression inventory score in the intervention group compared with the controls. The findings were similar at 8 and 12 months and there was no reduction in antidepressant use in the intervention group. Physical activity increased in that group.

The intervention increased levels of physical activity but did not relieve symptoms of depression.

Chalder M et al. Facilitated physical activity as a treatment for depressed adults: randomised controlled trial. *BMJ* 2012; 344 (June 9): 14 (e2758); Daley A, Jolly K. Exercise to treat depression. Ibid: 6 (e3181).

Relapse prevention in schizophrenia: antipsychotic drugs versus placebo

A systematic review and meta-analysis has led to the conclusion that maintenance treatment with antipsychotic drugs is beneficial in schizophrenia.

The analysis included 65 trials (6493 patients) comparing antipsychotic drugs with placebo in schizophrenia. Compared with placebo, antipsychotic drugs reduced relapse rates at 1 year significantly from 64% to 27%. Readmission rates were reduced significantly from 26% to 10%. There was a suggestion of better quality of life and fewer aggressive acts with the drugs. Antipsychotic drugs were associated with weight gain, movement disorders, and sedation. Depot preparations were more effective in reducing relapse than oral drugs and the most effective were depot haloperidol and fluphenazine.

Maintenance treatment with antipsychotic drugs is effective but the benefit must be weighed against adverse effects.

Leucht S et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012; 379: 2063-71; van Os J, Howes OD. Antipsychotic drugs for prevention of relapse. Ibid: 2030–1 (comment).

CPD Challenge

See page 62 to test yourself on this article