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STEP study: disappointing, but not a failure

On Sept 18, the independent data monitoring and safety board for the STEP (towards developing an HIV vaccine) trial convened for a pre-planned interim analysis. The trial was a randomised, double-blind phase II trial of an HIV vaccine sponsored by the HIV Vaccine Trials Network, the US National Institute of Allergy and Infectious Disease, and Merck & Co—the vaccine’s developer.

The vaccine, V520, uses a replication-defective adenovirus type 5 as a vector to deliver three synthetically produced HIV genes, gag, pol, and nef, and is designed to provoke an HIV-specific immune response mediated by CD8 T cells. The trial was designed to answer two questions: could the vaccine prevent HIV infection and, in those who did become infected, would the vaccine lower viral load. 3000 HIV-negative volunteers were enrolled in North and South America, the Caribbean, and Australia. All were from groups at high risk of HIV infection. All were counselled on ways to reduce their risk of HIV prevention. Initially, only patients with low titres to the adenovirus type 5 (Ad5), a common cold virus, were entered into the trial, but when testing indicated that there seemed to be no ill effects in patients who had evidence of prior immunity to Ad5, patients with higher titres were allowed to start the injections. A second “sister” study, called Phambili, which means “to move forward” in Xhosa, had recently been launched in South Africa.

The interim analysis focused only on volunteers from the low Ad5 titre group, who, because they had been injected earlier, were further along in the study. The findings were surprising—and disconcerting. Not only had the vaccine failed to prevent infection or to reduce viral load, but also further analysis suggested that the vaccine might have actually increased susceptibility to infection. Both the STEP study and the Phambili study were immediately halted and word of the results was promptly sent out to all the trial participants.

Researchers are already looking at the immune responses to the vaccine in these volunteers to determine why it seemed to be ineffective. And genetic studies of the virus are also underway to determine whether these strains were somehow capable of eluding the vaccine-generated immune responses.

Last week, at a meeting of the HIV Vaccine Trials Network in Seattle (Nov 7–8), trial investigators came together to discuss the trial’s findings. The data presented at the meeting were to be posted on the Network website by Nov 14.

In their presentation, the investigators repeatedly cautioned that much of what was discussed was preliminary, based on post-hoc analysis and small numbers. Of particular interest were analyses that suggest that volunteers who started the trial with higher titres against Ad5 and received the vaccine seemed to be more susceptible to HIV infection.

Why higher Ad5 titres might be associated with higher risk of infection clearly puzzled the investigators. If the association proves true, it might be, according to one hypothesis, that the Ad5 vector stimulates an immune system already primed for Ad5 and, as a result, expands the population of target cells for HIV, thus increasing the risk of infection. But it is also possible that Ad5 titres are, instead, an indirect marker of some other as yet unidentified biological, demographic, or behavioural factor. For example, fewer men in the study with higher Ad5 titres had been circumcised and they tended to live outside of the USA. And, given the low numbers involved, the findings related to Ad5 titres might be due to chance.

In any case, the trend associating susceptibility to HIV infection with higher Ad5 titres suggests that trial protocols that use this vector or other vectors might need to be redesigned so that they can help answer some of the questions raised about vectors by this study. The failure of the vaccine to provide protection or to reduce viral load also raises a more fundamental question: whether vaccines that only induce cell-mediated responses will prove effective.

Given the elusive nature of any HIV vaccine, it is important that other prevention measures are promoted vigorously, including HIV/AIDS education, condom programmes, and, to reduce the risk among intravenous drug users, needle exchange. Currently, fewer than 20% of the world’s population has access to effective HIV prevention programmes.

But though disappointing, the STEP study is not a failure. It shows that it is possible to work with diverse communities to do a well-designed trial that quickly answered the questions it was designed to, while at the same time protecting the safety of the volunteers. The investigators, clinical staff, and volunteers have reason to be proud to have been part of this trial. ■ The Lancet

For more on the HIV Vaccine Trial Network see http://www.htvn.org
For more on the Phambili study see http://www.phambili.org.za/

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IGWG suspended but must not stall

Last week, the Intergovernmental Working Group on Public health, Innovation and Intellectual Property (IGWG), involving representatives of 140 WHO member states, met with the aim of agreeing a global strategy and plan of action to stimulate research and development for diseases that disproportionately affect people living in poor countries. After 6 days of discussion, negotiation, and argument, the strategy and plan of action were not finalised, and the resumption of talks has been tentatively scheduled for Spring next year. Although the lack of a finalised plan is disappointing, it is unsurprising given that such agreement would signify a general consensus on several contentious issues, most notably intellectual property (IP).

The perplexing problem of IP has plagued IGWG since its conception after the World Health Assembly in May last year. For example, due to disagreements over IP, the USA was the only country not to endorse a resolution after this year’s Assembly which called for more support for the IGWG process. And a letter in this week’s issue discusses how the pharmaceutical industry influenced the draft strategy and action plan through patient advocacy groups and professional associations.

In her opening remarks to the IGWG session, Margaret Chan acknowledged that the negotiations would not be easy. However, the decision to suspend the talks rather than rush through the most controversial issues, such as IP, was seen as a positive step by most member states representing low-income and middle-income countries, and by many of the non-governmental organisations present. In addition, the inclusion of language which referred to an “R&D treaty” in the (still draft) strategy and action plan, despite vigorous opposition from the European Union, is also heralded as a step forward.

But as highlighted at the closing session by a representative from the Kenyan delegation, there must be tangible progress before the next meeting. People living in poor countries have the most to gain from the global strategy and plan of action but they also have the most to lose. The IGWG process must not be allowed to fail or falter however contentious the issues, and however forceful, or manipulative, the opposition.

Med abbrevs

Medical abbreviations can be useful, and even The Lancet has a limited list that it no longer spells (eg, AIDS and WHO). But abbreviations can also be annoying (what is MTCTP?) and occasionally dangerous (is MS morphine or magnesium sulphate; is AZT zidovudine or asazithioprine?). In texts, they are visually disturbing and stop the train of thought when reading.

The paediatric department at Birmingham Heartlands Hospital in the UK has just audited abbreviations. Joanna Sheppard and colleagues found that 25 shift-handover sheets had 2286 abbreviations in total, with a mean of 32 patients per sheet. 221 different abbreviations were found (a mean of 91 per sheet). When the authors compared the abbreviations against their hospital’s intranet dictionary and a medical dictionary used by paediatric secretaries, only 14% and 20%, respectively, were in the dictionaries. 14% and 11%, respectively, had differing meanings.

Luigi Brunetti and colleagues, from the Ernest Mario School of Pharmacy, Rutgers University, New Jersey, recently reviewed around 30 000 drug-error reports sent to a US national database over 3 years. Almost 5% of errors were attributable to abbreviations, including drug names and dose quantity and frequency, and nearly all the errors occurred during prescribing.

The Joint Commission, which has been accrediting health-care provision in the USA for over 50 years, has devised a “do not use” list of abbreviations in an attempt to reduce errors. The list includes any drug-name abbreviation, cc, μg, U and IU, qd and qod, and a ban on trailing zeroes after a decimal point in prescriptions. The commission has tips to eliminate these dangerous abbreviations, including lists displayed in records and near computers, on pocket cards for staff, and on prescription orders. Pharmacies, advises the Commission, should be directed not to accept any prohibited abbreviation.

For all their convenience, abbreviations can be confusing, ambiguous, and dangerous. They should be used sparingly, especially when prescribing. QED.
Fenofibrate for diabetic retinopathy

Diabetic retinopathy remains the leading cause of blindness and vision loss in adults aged under 40 years in the developed world. In today’s *Lancet*, Tony Keech and colleagues’ report results about laser treatment for diabetic retinopathy from the FIELD study. FIELD is the Fenofibrate Intervention and Event Lowering in Diabetes randomised trial.

The investigators’ aim in this latest FIELD report was to assess whether long-term lipid-lowering therapy with fenofibrate could reduce retinopathy progression in a large sample of patients (nearly 9800) with type 2 diabetes mellitus. The endpoint was the need for laser treatment (a tertiary endpoint of the main study) and the average follow-up was 5 years. In an intention-to-treat analysis, fenofibrate reduced the frequency of first laser treatment for macular oedema by 31% and for proliferative retinopathy by 30%. In a substudy of 850 patients who were able to be followed up to the close of the study, retinal status was graded by fundus photography, with an endpoint of two-step progression of diabetic retinopathy. In this substudy, fenofibrate reduced the risk of first laser treatment by more than 70%. However, only 28 patients required laser treatment (23 in the placebo group and five in the fenofibrate group). Also, the occurrence of new retinopathy or macular oedema, the progression of hard exudates, and worsening visual acuity were not reduced by fenofibrate. Only the progression of existing retinopathy was significantly reduced, but again the number of events was small (14 in the placebo group and three in the fenofibrate group).

The rationale for FIELD was that elevated lipid levels in the systemic circulation constitute a risk factor for diabetic retinopathy. However, whereas there is some evidence to implicate serum lipids in exudative maculopathy, that for the effects of lipids on the development or progression of diabetic retinopathy overall is less consistent. Additionally, there have been only a few prospective studies, and it is unclear to what extent a previously observed relation might be confounded by the degree of hyperglycaemia. In fact, in today’s FIELD report, the investigators found no relation between serum lipids and the appearance or progression of diabetic retinopathy. In recent years, new insights have been gained into the transport of lipids within the retina, which allow us to hypothesise that the mechanisms regulating intraretinal lipid transport rather than serum levels might be more important in the pathogenesis of diabetic retinopathy. In this regard, in a proteomic analysis of human vitreous fluid, we have found that apolipoprotein A1 and apolipoprotein H were produced intraocularly in high concentrations in patients with proliferative diabetic retinopathy compared with non-diabetic individuals.

Tight control of blood glucose levels and hypertension, argon-laser retinal photocoagulation, and vitreoretinal surgery are the main therapies for diabetic retinopathy. As we learn more and more about the molecular mechanisms in the pathogenesis of diabetic retinopathy, new therapeutic products have been developed. The protein kinase C inhibitor, ruboxistaurin mesilate, administered orally was effective in halting diabetic macular oedema and vision loss but not in preventing progression of diabetic retinopathy. But, because the primary endpoint was not achieved, initial enthusiasm for ruboxistaurin mesilate has evaporated. A phase III clinical study with a long-acting somatostatin analogue (octreotide) given intramuscularly in patients with moderate-to-severe non-proliferative or with low-risk proliferative diabetic retinopathy ended more than 2 years ago but the results have yet to be published. Antagonists of vascular endothelial growth factor
administered by intravitreous injections have been used successfully in age-related macular degeneration, but phase III trials specifically looking at diabetic retinopathy are still needed. In this regard, a sample at higher risk or a follow-up even longer than 5 years would be necessary. On the other hand, the mechanisms by which fenofibrate exerts its reported benefits are far from being elucidated. For all these reasons, further clinical and experimental studies are needed before fenofibrate can be launched as a new tool in the management of diabetic retinopathy.

Reduction of HIV-1 drug resistance after intrapartum single-dose nevirapine

Few issues in mother-to-child HIV-1 transmission have sparked as much controversy as intrapartum single-dose nevirapine. This drug is 40% efficacious in the prevention of such transmission, easy to use, safe, and cheap, which are all especially important in the developing world, where half a million children are infected annually by this route. But, by 2006, only 11% of HIV-infected women in sub-Saharan Africa were receiving antiretroviral drugs to prevent transmission to their children. The obstacles there include limited antenatal care: only two-thirds of pregnant women have at least one antenatal visit with a nurse or doctor, and under half have four or more. However, single-dose nevirapine programmes can be effectively implemented in these settings.

After single-dose nevirapine, 19–75% of women and 33–87% of the minority of infants who become infected develop virus that is resistant to non-nucleoside reverse-transcriptase inhibitors (NNRTIs). Combination of other antiretrovirals with single-dose nevirapine somewhat attenuates the emergence of nevirapine resistance (figure). The TOPS study from South Africa showed that addition of intrapartum plus 4–7 days of maternal postpartum zidovudine significantly reduced detectable nevirapine resistance (from 57% to 9–13%) in women who did not receive any antenatal antiretrovirals.
NNRTIs are a component of first-line antiretroviral regimens throughout the world. Resistance that arises after single-dose nevirapine can compromise response to subsequent maternal treatment with nevirapine-based antiretrovirals, although the problem is less in women who start antiretrovirals 6 or more months after taking single-dose nevirapine. Maternal combination prophylaxis regimens are also more effective at preventing vertical transmission than is single-dose nevirapine alone, and some practitioners therefore believe the latter should not be used at all—even though it may be the only feasible intervention in many areas.

In today’s *Lancet*, Benjamin Chi and colleagues present new and encouraging data from Zambia to show that addition of one intrapartum dose of tenofovir/emtricitabine to short-course zidovudine plus single-dose nevirapine significantly reduced the prevalence of detectable nevirapine-resistant maternal virus at 6 weeks’ postpartum. In the subgroup of women with sequences available for analysis at 6 weeks’ postpartum, 30% of 138 women in the control group compared with 14% of 147 women in the intervention group harboured nevirapine-resistant virus. Importantly, mutations associated with resistance to tenofovir or emtricitabine were not detected at any time.

In Chi and colleagues’ study, only women with less advanced HIV-1 disease (who did not qualify for combination antiretrovirals) were eligible to enter. Also, 81% of participants also took short-course zidovudine (for a median of about 37 days) before single-dose nevirapine (in either group). Both these factors might have reduced the median maternal HIV-1 RNA levels at delivery. Because higher HIV-1 RNA at delivery has been associated with greater risk for selection of resistance after single-dose nevirapine, the relative risk of developing nevirapine resistance might be different in settings in which women do not have access to or present too late in pregnancy to receive antenatal antiretrovirals (as recommended by WHO and used by Chi).

Chi and colleagues classified maternal samples with HIV-1 RNA levels below 2000 copies per mL (not genotyped due to low yield) as harbouring no resistance in the primary analysis, rather than omitting them from the analysis altogether as would generally be done. The analysis as done could lead to underestimation of the prevalence of resistance, particularly in the intervention group at 2 weeks, in view of the transient suppression of viral load that was associated with being on tenofovir/emtricitabine. The secondary analysis which omitted samples that were not genotyped might be more valid.

We also need to learn about the incidence of nevirapine resistance in infants who become HIV-1 infected despite the addition of tenofovir/emtricitabine to zidovudine and single-dose nevirapine. Since Chi and colleagues’ study was conceived, new data have somewhat allayed concerns about the clinical implications of maternal nevirapine resistance after single-dose nevirapine, but resistance in HIV-infected infants may have more dire implications for subsequent paediatric response to nevirapine-based treatment. Additionally, although the clinical implications of minority resistant variant populations are unknown, future studies of the presence of such variants after the addition of single-dose tenofovir/emtricitabine will be important, particularly to assess for resistance to emtricitabine. It would be of concern if the use of single doses of both tenofovir/emtricitabine and nevirapine resulted in large proportions of patients developing even low-level resistance to both emtricitabine and nevirapine, which might affect subsequent response to treatment with
these commonly used classes of drugs. Finally, although it is unlikely that one dose of tenofovir given to a mother and newborn infant is associated with important toxic effects in infants (including adverse effects on bone development), the safety of in-utero exposure to tenofovir is being examined.

The question today is under what circumstances single-dose tenofovir/emtricitabine should be used as part of a regimen to prevent mother-to-child transmission of HIV, in view of Chi and colleagues’ data. Combination three-drug prophylaxis might in the future be increasingly available to all pregnant HIV-1-infected women regardless of CD4+ cell count, which would make single-dose nevirapine obsolete. Currently, however, most women either do not receive any intervention at all, or take only single-dose nevirapine. Chi’s results cannot necessarily be extrapolated to women who take only nevirapine without antenatal zidovudine, for the reasons noted above. However, WHO recommends that women with less advanced HIV (who comprise the majority of HIV-infected pregnant women) be given short-course zidovudine with single-dose nevirapine (with a 7-day tail of zidovudine plus lamivudine).22 Chi’s results do provide strong evidence that addition of single-dose tenofovir/emtricitabine to short-course zidovudine and single-dose nevirapine in women with higher CD4+ cell counts is a new, effective, and feasible approach to reducing maternal nevirapine resistance, and one that should be seriously considered for implementation.

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We declare that we have no conflict of interest.


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Depression and anxiety with rimonabant

The first endogenous cannabinoid was isolated in the early 1990s, followed soon after by identification of the endocannabinoid receptors CB₁ and CB₂. Clinical observations that cannabis stimulates appetite (the “munchies”) suggested that the endocannabinoid system is involved in the control of energy balance.¹ Rimonabant, the first of the CB₁-receptor antagonists to be marketed, was developed as an anti-obesity agent on the premise that blocking central cannabinoid activity might reduce food intake.² Its efficacy for weight reduction was shown by a series of major reports.³,⁴

In a meta-analysis of the four pivotal RIO (Rimonabant In Obesity) studies in today’s Lancet, Robin Christensen and colleagues provide compelling evidence that rimonabant is associated with development of severe adverse psychiatric events.⁵ Participants who received rimonabant 20 mg were 2.5 times (95% CI 1.2–5.1; p=0.01) more likely than those who took placebo to discontinue treatment because of depression or depressive symptoms (3.0% vs 1.4%) and 3.0 times (95% CI 1.1–8.4; p=0.03) more likely to discontinue treatment because of anxiety (1.0% vs 0.3%). Furthermore, rimonabant was associated with significantly increased anxiety (odds ratio 3.03, 95% CI 1.09–8.42), as measured on the Hospital Anxiety and Depression Scale. These findings are especially striking since people who had a history of serious depression or other psychiatric illnesses had been excluded before study entry and people with severe obesity have been shown to be at high risk of depression.⁶

Submission of Christensen and colleagues’ report to The Lancet coincided with release of a report by an Advisory Committee of the US Food and Drug Administration (FDA),⁷ which also raised major concerns that rimonabant might be linked to adverse psychiatric events. In fact, the FDA report suggested that Christensen could have underestimated the magnitude of psychiatric complications of this drug, because the published trials did not provide detailed data on rates of psychiatric adverse effects. Examining the same four studies, the FDA Committee found that 26% of participants who took rimonabant 20 mg had an adverse psychiatric event (mainly anxiety or depression) compared with 14% of those who took placebo. This increase in psychiatric complications with rimonabant (relative risk 1.9) was significant compared with placebo (95% CI 1.5–2.3). Survival analysis showed that these adverse events developed early in treatment. Moreover, in a broader suite of rimonabant studies, the FDA identified substantial evidence for an increased risk of suicide attempts or suicidal ideation in participants who took rimonabant 20 mg compared with placebo (odds ratio 1.9, 95% CI 1.1–3.1).

These clinical findings coincide with reports of animal studies that implicate the CB₁ receptor in mediation of antidepressant-like or anxiolytic-like effects of the endocannabinoid system. Inhibition of the breakdown of the endogenous cannabinoid anandamide has an antidepressant-like effect in rodents; this effect was blocked by rimonabant.⁸ In rodents exposed to stress induced by swimming, another CB₁ antagonist (AM251) impaired the reduction in corticosterone secretion that results from exposure to tricyclic antidepressants.⁹ Mice that were either genetically deficient for an enzyme (fatty acid amide hydrolase) that degrades anandamide or received a specific inhibitor of this enzyme displayed reduced anxiety-like behaviour; moreover, this effect was blocked by rimonabant.¹⁰ These studies consistently showed that pharmacological blockade of the CB₁ receptor impaired the antidepressant-reducing or anxiety-reducing actions of endocannabinoids. However, some discrepancies in
animal studies should be acknowledged, since some reports have suggested that rimonabant might have antidepressant or anxiolytic actions. Another observation that might provide an alternative physiological basis for increased mood disorders seen with greatest weight-loss comes from evidence that leptin, the adipose-derived hormone, had an antidepressant action after intrahippocampal but not hypothalamic injection. However, direct clinical correlates are difficult to draw.

What is the significance of the findings reported by Christensen and colleagues? First, their meta-analysis has raised major questions about the safety of rimonabant in obese people, who are already at an increased risk of depression, especially since the FDA review suggests that the risk of suicide is increased by use of this agent. Moreover, at least four other companies have CB, antagonists in phase II or III development. The findings of Christensen and colleagues’ meta-analysis suggest that phase III studies of such CB, antagonists should monitor psychiatric complications very carefully. Second, the link between depression and this CB1-receptor blocker raises theoretical questions about a potential central role for the endocannabinoid system in both normal and clinical mood states.

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Benefits and risks of homoeopathy

Five large meta-analyses of homoeopathy trials have been done. All have had the same result: after excluding methodologically inadequate trials and accounting for publication bias, homoeopathy produced no statistically significant benefit over placebo. And yet homoeopathy can still be clinically useful.

During the cholera epidemic in the 19th century, death rates at the London Homoeopathic Hospital were three times lower than those at the Middlesex Hospital. The reason for homoeopathy’s success in this epidemic is even more interesting than the placebo effect. At the time, nobody could treat cholera, and while medical treatments such as blood-letting were actively harmful, the homoeopaths’ treatments were at least inert.

Similarly, modern medicine can offer little for conditions such as many types of back pain, stress at work, medically unexplained fatigue, and most common colds. Going through a theatre of medical treatment, and trying every drug in the book, will only elicit side-effects. An inert pill in these circumstances seems a sensible option.

However, just as homoeopathy has unexpected benefits, so it can have unexpected side-effects. The very act of prescribing a pill carries its own risks: medicalisation, reinforcement of counterproductive illness behaviours, and promotion of the idea that a pill is an appropriate response to a social problem, or a modest viral illness.

Similarly, when a health-care practitioner of any description prescribes a pill which they know is no more effective than placebo—without disclosing that fact to...
their patient—then they disregard both informed consent and their patient’s autonomy. Some could argue that this cost is acceptable, but such old-fashioned paternalism can ultimately undermine the doctor-patient relationship.

There are also more concrete harms. A routine feature of homoeopaths’ marketing practices is to denigrate mainstream medicine. One study found that half of all homoeopaths who were approached advised patients against the measles, mumps, and rubella vaccine for their children.7 A television news investigation found that almost all homoeopaths who were approached recommended ineffective homoeopathic prophylaxis for malaria, undermined medical prophylaxis, and did not even give simple advice on bite prevention.8 Undermining medicine is a wise commercial decision for homoeopaths, because survey data show that a disappointing experience with mainstream medicine is one of the few features to regularly correlate with a decision to use alternative therapies. But it might not be a responsible choice.

Homoeopaths can undermine public-health campaigns; leave their patients exposed to fatal diseases; and, in the extreme, mis or disregard fatal diagnoses. There have also been cases of patients who died after medically trained homoeopaths advised them to stop medical treatments for serious medical conditions.9,10 All these problems have been exacerbated by society’s eagerness to endorse the healing claims of homoeopaths, and by the lack of a culture of critical self-appraisal in alternative medicine. Publication bias in alternative therapy journals is high: in 2000, only 5% of studies published in complementary or alternative health journals were negative.11 To my knowledge, the ethical issues of autonomy and placebo have never been discussed. Homoeopaths routinely respond to negative meta-analyses by cherry-picking positive studies. An observational study,12 which amounts to little more than a customer-satisfaction survey, has been promoted13 as if it trumps a string of randomised trials.

Homoeopaths can misrepresent scientific evidence freely to an unsuspecting and scientifically illiterate public, but in doing so they undermine the public understanding of what it means to have an evidence base for a treatment. This approach seems particularly egregious when academics are working harder than ever to engage the wider public in a genuine understanding of research,14 and when most good doctors try to educate and involve their patients in the selection of treatment options.

Every criticism I have made could be managed with clear and open discussion of the problems. But homoeopaths have walled themselves off from academic medicine, and critique has been all too often met with avoidance rather than argument. The Society of Homeopaths (in Europe) has even threatened to sue bloggers,15 and the university courses on alternative medicine which I and others have approached have flatly refused to provide basic information, such as what they teach and how.16 It is hard to think of anything more unhealthy.

To ban homoeopathy would be an over-reaction, as placebos could have a clinical role. However, whether the placebo effect is best harnessed by homoeopaths will remain questionable until these ethical issues and side-effects have been addressed.

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I am a medical doctor who is also employed by the media as a commentator on pseudoscience and the sociology of medicine.

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Clinical update: postpolypectomy colonoscopy surveillance

Most colorectal cancers arise from adenomatous polyps. During colonoscopy, adenomatous polyps are typically removed by polypectomy, and patients undergo periodic surveillance colonoscopy because of the increased risk of metachronous adenomas. Here we discuss the rationale behind current guidelines for such surveillance, but not surveillance after curative treatment of colorectal cancer or in patients with inflammatory bowel disease or genetic syndromes such as hereditary non-polyposis colorectal cancer. The US Multi-Society Task Force on Colorectal Cancer, representing the positions of the American Gastroenterological Association and American Cancer Society, provide a recent and long review.

The increased risk of recurrent adenomas after polypectomy results from lesions missed during the initial colonoscopy as well as a true increased risk of developing de-novo neoplastic lesions due to environmental and genetic risk factors particular to the patient. In other words, the initial adenoma serves as a marker for increased risk of colorectal neoplasia. The 1-year recurrence rate for small adenomas is 11%, on the basis of a study that used tandem colonoscopy to adjust for the effects of missed polyps. Current surveillance guidelines are based on risk stratification. Low-risk patients (ie, those with only one or two small adenomas) have an overall risk of 3–11% for developing metachronous advanced neoplasia 3 years after the initial colonoscopy and polypectomy. Intermediate-risk patients include those with multiple small adenomas (relative risk of 2.52 for advanced neoplasia at 3 years), large adenomas (1.39), tubulovillous or villous adenomas (1.26), or adenomas with high-grade or intermediate-grade dysplasia (1.78). High-risk patients are those with large sessile adenomas or more than ten adenomas. Depending on the risk, different surveillance intervals are recommended.

Most of the data on the efficacy of surveillance comes from observational studies in patients who had polypectomy and subsequent surveillance. Because of the design of these studies, it is difficult to separate the effect of the initial polypectomy from that of the follow-up surveillance, but modelling estimates that as much as 90% of the benefit could be derived from the initial polypectomy. The National Polyp Study showed a 76% reduction in the incidence of colorectal cancer over about 6 years in patients who had had polypectomy followed by colonoscopic surveillance at 1 or 3 years, when compared with the expected incidence from the Surveillance, Epidemiology and End Results (SEER) programme. In the Norwegian Telemark Polyp Study, patients who had had polypectomy and colonoscopic surveillance at 2 and 6 years had an 80% reduction in the incidence of colorectal cancer over 13 years compared with randomly selected controls; however, the small sample size makes interpretation difficult.

By contrast, data from several randomised chemoprevention trials, primarily designed to assess the effect of aspirin, antioxidant vitamins, calcium, or dietary fibre on the incidence of colorectal cancer, show no reduction in incidence compared with SEER data. In these studies, patients had a baseline colonoscopy with polypectomy of at least one adenoma and then surveillance colonoscopy at 1 and 3–4 years. The discrepant results between the National Polyp Study and the chemoprevention trials might be because the former excluded patients with large sessile polyps and took steps to guarantee the adequacy of the baseline “clearing” colonoscopies (eg, two tandem colonoscopies, on the same day, were required in 13% of patients). Furthermore, unlike the National Polyp Study, the chemoprevention trials mandated surveillance colonoscopies at the end of follow-up for each patient, thus facilitating the detection of small asymptomatic cancers. Both groups of studies excluded patients with colorectal cancer at entry, which potentially inflates the polyp-reduction effect of polypectomy and surveillance when compared against SEER data.

The table shows current guidelines from major organisations, including the US Multi-Society Task Force on Colorectal Cancer (the Task Force), the American College of Gastroenterology (ACG), the American Society of Gastrointestinal Endoscopy (ASGE), and the British Society of Gastroenterology (BSG). In general, the guidelines are similar. All guidelines rely on periodic colonoscopy as the primary method of surveillance. The surveillance interval is based on the risk of metachronous adenomas as predicted by findings on initial colonoscopy. Most guidelines recommend repeat colonoscopy in 3–10 years for low-risk patients (only one or two small adenomas, <1 cm in size); for such
patients, the BSG advises either repeat colonoscopy in 5 years or no surveillance at all (ie, patients can continue average-risk screening). For patients at intermediate risk (advanced neoplasm or multiple [3-10] small adenomas), colonoscopy should be repeated in 3 years, with subsequent colonoscopies every 5 years if the preceding colonoscopy was negative. In most of the guidelines, an advanced neoplasm is defined as a villos or tubulovillous adenoma, an adenoma with intermediate-grade or high-grade dysplasia, or a tubular adenoma 1 cm in size or larger. The Task Force guidelines specify that colonoscopy intervals can be extended to 10 years if the preceding colonoscopy did not show adenomas. In patients with numerous (>10) adenomas but no overt adenomatous polyposis syndrome, colonoscopy should be repeated in less than 3 years, the exact interval to be determined by the endoscopist. For patients with large sessile adenomas that are difficult to remove completely in one session, a repeat colonoscopy after a short interval (2–6 months) is recommended. Subsequent intervals are customised according to the level of suspicion for residual adenomatous tissue at the polypectomy site. If the sessile polyp is very extensive or has high-grade dysplastic features, surgical resection should be considered. After it is certain that all adenomatous tissue has been removed, surveillance with 3–5 year intervals can be resumed.

Over the past few decades, recommended intervals between surveillance colonoscopies have been extended, on the basis of accumulating data which show that longer surveillance intervals are safe. For example, the National Polyp Study showed no difference in adenoma risk between patients who had repeat colonoscopy at 1 year versus those who had colonoscopy at 3 years, while the Funen Adenoma Study showed no statistically significant difference in adenoma recurrence rates at 4 years compared with 2 years. More recently, a German case-control study has supported a 5-year surveillance interval. Depending on patient’s physician’s preference, surveillance may be discontinued if life expectancy is under 10 years (Task Force) or if the patient is over 75 years old (BSG). For most guidelines, surveillance recommendations are relaxed after one or two negative follow-up colonoscopies. However, the ACG considers those patients with a history of adenomas to be at lifelong risk for metachronous lesions and recommends colonoscopies at least every 5 years indefinitely. It is important to note that these surveillance interval recommendations are based on the assumption that the baseline colonoscopy is of high quality, with good bowel preparation, thorough removal of polyps, adequate examination time, and complete visualisation of all colonic mucosa up to and including the caecum.

Surveys have shown that patients’ compliance with physicians’ recommendations for surveillance is high (up to 85%), particularly in the presence of multiple or larger polyps. Also, patients are often interested in chemopreventive measures, such as antioxidants, fibre, and calcium or other dietary supplements, although efficacy has not been unequivocally shown for all these agents. The effect of surveillance colonoscopy on quality of life has not been directly studied, although
patients probably derive benefit if we extrapolate results from quality-of-life studies on screening colonoscopy.\textsuperscript{15} Unfortunately, many clinicians do not adhere to surveillance guidelines, often doing colonoscopies more frequently than recommended.\textsuperscript{17} This overuse is probably due to concerns about missed lesions or interval cancers, which can occur even in patients under close surveillance.\textsuperscript{2} Improved adherence to guidelines could be achieved by the use of reminder devices and algorithms for continuous improvement.\textsuperscript{18} Other screening measures, such as the use of interval testing of faecal occult blood,\textsuperscript{19} might also allow practitioners to feel more comfortable with longer surveillance intervals.

For the best return on colonoscopic capacity, most medical societies have recommended that surveillance guidelines be rigorously followed, to shift colonoscopic resources from surveillance to screening and diagnosis. This shift will also mitigate the cumulative complication risk, which becomes considerable with frequent colonoscopies.\textsuperscript{20} One of the main differences between recent and older Task Force recommendations is that surveillance intervals in patients with only one or two small adenomas have been lengthened to 5–10 years.\textsuperscript{2} This seemingly minor change will have a large effect on colonoscopic utilisation because low-risk patients represent the largest subgroup who might need surveillance. Further research will help define the best surveillance intervals, as well as the role of technical innovations such as computed tomographic colonography, chromoendoscopy, and narrow-band imaging.

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I declare that I have no conflict of interest.

Homoeopaths in the UK have been feeling under pressure lately. Unfortunately for them, however, the cause of their anxiety is not a heavy workload but an active campaign against homoeopathy, particularly its availability in the UK’s National Health Service (NHS). Over the past 2 years, journalists, doctors, and scientists, who point to the lack of evidence for the effectiveness of homoeopathy, have publicly voiced their criticisms.

The latest subject to irk antihomoeopathy campaigners is a symposium on the role of homoeopathy in HIV/AIDS treatment that is taking place in London on Dec 1, organised by the Society of Homeopaths—the largest organisation representing lay homoeopaths in Europe. “The symposium will be looking at different methods and approaches that appear to be having some success in helping with the symptoms of HIV/AIDS”, say the organisers. Michael Baum, professor emeritus of surgery at University College London and frequent critic of homoeopathy, thinks that homoeopaths are getting overconfident. “People say homoeopathy cannot do any harm but when it is being promoted for HIV then there is a serious problem”, he says.

Baum is not alone in his concern about the potential dangers of homoeopathy. Last year, an undercover investigation by charity Sense About Science, showed that the first ten homoeopathic clinics and pharmacies selected from an internet search and consulted were willing to provide homoeopathic pills to protect against malaria and other tropical diseases such as typhoid, dengue fever, and yellow fever. “Making false claims about malaria”, says David Colquhoun, professor of pharmacology at University College London.

Both Colquhoun and Baum are among a group of doctors and scientists who, last May, sent a letter to Primary Care Trusts (the local bodies that pay for NHS care) in the UK to raise their concerns about the use of homoeopathy on the NHS. “It is an implausible treatment for which over a dozen systematic reviews have failed to produce convincing evidence of effectiveness”, they wrote. Baum says that the group have received a lot of criticism for issuing the letter and have even been accused of colluding with the pharmaceutical industry over their antihomoeopathy campaign. “But”, he says, “the reason that we started this campaign was out of a sense of despair over a malaise in society, a flight from rationalism”.

Their actions seem to be having an effect. In September, West Kent Primary Care Trust decided to stop NHS funding for the Tunbridge Wells Homoeopathic Hospital—one of five hospitals that provide homoeopathy on the NHS. In a press statement, James Thallon, the Primary Care Trust’s medical director, said: “…it is the clear duty of PCTs [Primary Care Trusts] to make best use of public money by commissioning clinically cost-effective care…There is not enough evidence of clinical effectiveness for us to continue to commission homoeopathy”.

The Royal London Homoeopathic Hospital is also feeling the backlash. Several Primary Care Trusts have stopped, or drastically reduced, their funding of treatment at the hospital. Peter Fisher, clinical director at the hospital, says referrals were down by around 20% in October compared with the same month last year. Although he admits that the “evidence base is not as strong as we would like” for homoeopathy, he says, that “patients are our best advocates. They tell us that we have helped them when nothing else could”.

Indeed, homoeopathy, which has been available on the NHS since it began in 1948, remains ever popular with the UK public. Around 13 000 patients are treated at the five homoeopathic hospitals each year and 14.5% of the population say they trust homoeopathy.

The UK homoeopathic market is predicted to be worth £46 million in 2012.
Referrals to the Royal London Homoeopathic Hospital are down

homoeopathic medicines. According to the market research group Mintel, the homoeopathy market is estimated to be worth £38 million and is projected to reach £46 million in 2012.

Baum thinks that public support for homoeopathy might be because people often confused it with herbal medicine. Although many herbal medicines are unproven, they have scientific plausibility, unlike homoeopathy, where often remedies are given in such a highly diluted form that not even a single molecule of active ingredient is left. Homoeopaths believe that dilution increases, not decreases, the strength of a remedy. They also treat like with like, so an illness is treated with a natural substance which could produce similar symptoms in a healthy person. For example, a homoeopathic remedy for insomnia might include caffeine.

A meta-analysis published by The Lancet in 2005, and four other large meta-analyses, have shown that the clinical effects of homoeopathy are no greater than placebo. Controversially, some commentators think there might be a future in prescribing homoeopathy because of its placebo effect. But Baum disagrees. He thinks that knowingly prescribing placebos is “unethical and patronising”. He believes that improving the communication skills of conventional doctors can improve patients’ experiences with clinically effective treatments, since they come with the added bonus of a placebo response.

Both the Society of Homeopaths and the Faculty of Homoeopaths—the professional body for doctors and other health professionals who integrate homoeopathy into their practice—disagree with the findings of the Lancet study. They believe that the effect of homoeopathy is greater than placebo and that the dilute homoeopathic remedies themselves exert an effect. “There are many scientists around the world who have found evidence that water may retain information about homoeopathically prepared solutes”, said a Faculty spokesperson. Baum cannot understand how anyone with scientific training, can believe in the principles and theories behind homoeopathy. “They seem to be able to divide their brain into two parts—rational and irrational”, he says.

But perhaps scientific training is not what it used to be. Six universities in the UK now offer Bachelor of Science degrees in homoeopathy, according to a news feature published in Nature in March. In an accompanying commentary, David Colquhoun wrote that homoeopathy “has barely changed since the beginning of the nineteenth century. It is much more like a religion than science”. Although most of the universities that teach complementary medicine have refused to show their teaching materials to Colquhoun, some have said they teach homoeopathy alongside more traditional subjects such as physiology. “The poor kids must be very confused”, he says. “One day they are learning the bigger the dose the greater the effect, the next day they are learning that the smaller the dose the greater the effect.”

Despite being slammed by many scientists and doctors, homoeopathy has received a recent boost from an unexpected quarter. In September, 2006, the Medicines and Health Regulatory Agency—the government agency that is responsible for ensuring that medicines work, and are acceptably safe—introduced regulations that supported the use of homoeopathic over-the-counter remedies for some conditions. The new licensing scheme, to the dismay of many scientists and doctors, allows manufacturers of homoeopathic remedies to indicate what conditions their products could be used for. But, unlike conventional medicines, manufacturers only have to provide safety evidence and information about what their remedies are traditionally used for to gain a licence. Baum says, “I don’t know what external pressures have been put upon them to go ahead with these new regulations. When I spoke to them they said it was for self-limiting conditions—insomnia, constipation. But I told them that insomnia can be a sign of acute depression and constipation can be a sign of colorectal carcinoma”.

Baum thinks that the only way forward is for the UK’s National Institute for Health and Clinical Excellence (NICE)—the independent organisation responsible for providing clinical guidance on treatments in England, Wales, and Northern Ireland—to assess the cost-effectiveness of homoeopathy. The topic would have to be referred to NICE by the Department of Health for this to happen.

The Department of Health told The Lancet that NICE already “consider complementary therapies alongside conventional treatments when developing clinical guidelines”. So far none of NICE’s existing clinical guidelines recommend homoeopathy for any condition.

Baum thinks specific guidance on homoeopathy as a whole is still needed. “I had to wait 2 years for breast cancer treatments I knew to be effective to be approved by NICE. Why is there a double standard with homoeopathy?”

Udani Samarasekera
Homoeopathy booming in India

In India, where homoeopathy is a national medical system, the market is growing at 25% a year, and more than 100 million people depend solely on this form of therapy for their health care, the popularity of the dilute remedies shows no signs of abating. Raekha Prasad reports.

In the western Indian state of Maharashtra, Shantaram Chavan, a poor farmer diagnosed as HIV positive, responded in desperation to an advertisement in a local newspaper placed by Siddharth Jondhale, a homoeopathic doctor, who said he had found a cure for the virus. For 1 year, Chavan took the drug administered by Jondhale at his private clinic. He sold his tractor to raise the 150 000 rupees (US$3800) to pay for the so-called miracle cure that Jondhale named HIV-SJ. During that year, the farmer’s condition deteriorated.

India has the world’s third highest caseload of HIV/AIDS after Nigeria and South Africa. Jondhale’s clinic drew in hundreds—all of whom had seen one of his leaflets or read his website that claimed he had cured 4000 people with HIV in the past 2 years. Last month, the law finally caught up with Jondhale and he was prohibited from advertising the fanciful claims. He is currently under investigation by medical authorities.

The case, which made headlines in the national press, highlighted the widespread acceptance of homoeopathy in India as a viable treatment for the most serious of diseases. Around 10% of India’s population—more than 100 million people—depend solely on homoeopathy for their health care, according to the Indian government.

The nation has almost a quarter of a million registered homoeopathic doctors—more than any other country in the world. The result is a permissive medical culture which sees “natural treatments” put on a par with scientific ones. Homoeopathy has become deeply rooted in India’s public health provision—it has the third largest government-supported infrastructure after ayurvedic and modern medicine.

The Indian government has almost 11 000 homoeopathic hospital beds and three-quarters of all registered practitioners have been trained by the state. Medical students, regardless of whether they intend to be homoeopaths or modern medics, share the first 3 years of training. The result is that India’s ailing public-health system faces competition from not only a well resourced private sector in conventional medicine but also a cheaper, widely available homoeopathic service. A visit to a homoeopathic doctor costs less than half the price charged by a medical doctor in India.

Another attraction is homoeopathy’s reputation of being harmless, SP Singh, the Ministry of Health and Welfare’s adviser on homoeopathy told The Lancet. “It does not give side-effects. With a small quantity of medicine we can serve a lot of people.” Despite evidence to the contrary, Singh says that homoeopathy “has a biological effect” and that “all homoeopathic medicines are therapeutically proven”. India is arguably unique in the extent to which it has recognised homoeopathy as a legitimate system of medicine. Despite originating in Germany, the Indian government has bestowed it with the status of a national medical system. India is also unusual in that it has seven national medical systems of which modern medicine is but one. Also recognised and administered by a special state department under the Ministry of Health and Family Welfare are ayurveda—India’s traditional medical treatment—yoga, naturopathy, unani—a system dating back to ancient Greece, siddha, one of India’s oldest health therapies from the south, and homoeopathy.

The department, known by the acronym Ayush, has a budget of 10 billion rupees ($260 million) over 5 years. “Money is not a problem”, said Singh. “It will be spent on education, training, standardisation of drugs, implementation of health programmes, and rural health care.”

Singh’s defence of homoeopathy sits uneasily with the conventional, scientific approach to medicine. The Indian government adviser says that homoeopathy gives patients options...
German missionaries introduced homoeopathy to India 200 years ago and is complementary to modern drugs. “In cases of crisis management allopathic is better, but if you have digestive problems then maybe [homoeopathic] is better. It is up to people to choose what they like.”

Homoeopathy is included under the umbrella department that is foremost intended to develop and sustain Indian health systems because of the notion that it shares some of the key characteristics of indigenous ancient medicine. “It has blended so well into the roots and traditions of the country that it has been recognised as one of the National Systems of Medicine and plays an important role in providing health care to a large number of people”, the government website states.

Homoeopathy was first brought to India almost 200 years ago by German missionaries who distributed remedies in Bengal. But it was not until 1839 when John Honigberger, a Romanian homoeopath and disciple of the father of homoeopathy, Samuel Hahnemann, successfully treated the then ruler of Punjab, Maharaja Ranjit Singh, in Lahore that homoeopathy gained the royal patronage that enabled it to take root in India.

Health experts, however, are concerned that many homoeopathic and ayurvedic doctors administer pharmaceutical drugs to their patients. “They [homoeopathy and ayurveda] provide a back-door entry into medicine. Those who don’t get into medical colleges try to get into general practice in rural areas through the other systems”, says Amar Jesani, an editorial board member of the Indian Journal of Medical Ethics.

The issue came to light in a high-profile case that reached India’s highest court in 1996, after a patient died after a registered and qualified private homoeopath gave him a cocktail of antibiotics—including drugs for typhoid. The court awarded the deceased’s spouse compensation and ruled the doctor guilty of negligence. The Supreme Court held that cross-practising amounted to quackery, stating: “a person who does not have knowledge of a particular system of medicine but practices in that system is a quack and a mere pretender to medical knowledge or skill, or a charlatan”. Despite the ruling, cross-practising persists. As many as 90% of doctors qualified in a system other than modern medicine are administering pharmaceutical drugs, according to the 52nd round of India’s National Sample Survey.

Apart from a growing pool of doctors trained in homoeopathy, the therapy's appeal is also due to the failure of the Indian public-health system which is ill equipped to serve the country’s vast population. According to the UN Development Programme, India has just 48 physicians per 100 000 people. The poor provision means people turn to the private sector, both modern and homoeopathic, which is lightly regulated.

However, medical physicians, say experts, are concentrated not only in private practice but also in predominantly wealthy urban India. This distribution again compounds the problem because poor people in rural areas, who make up most of India’s population, are left with little choice but to visit the cheaper, more accessible homoeopaths or ayurvedic doctors. “The government of India does not have incentives for allopathic doctors to go to rural areas. There is one doctor for every 250 people in Bombay and one for 10 000 people in a rural area a few hundred kilometres away”, says Jesani.

Like their contemporaries in the west, say health researchers, wealthy Indians see homoeopathy as a route to wellbeing. The result is a booming domestic industry, which has given rise to several corporate homoeopathic services. Estimated to be worth 6·3 billion rupees ($165 million) this year, the homoeopathy market is growing at 25% a year and within a decade spending on private homoeopathy will be almost 60 billion rupees ($1555 million). “An elite group of upper-middle and rich classes in India consider homoeopathy to be fashionable. This has led to corporatisation”, said Ravi Duggal, an independent health consultant in Mumbai. “Ethics are not on the agenda in [Indian] medicine. Making money is.”

However, companies say that homoeopathy needs to be professionalised to dispel the image that treatments are merely low-cost quackery. Mukesh Batra, who founded India’s largest homoeopathic chain of clinics—Dr Batra’s—said most of his patients came for chronic conditions and that “15% have terminal illnesses”. Batra says his clinics treat 130 000 people a year and his cyber clinic, which e-mails treatment plans and sends homoeopathic medicine in the post to patients, treats another 450 000 worldwide. The homoeopathy is keen to break into new markets—even if national laws are designed to keep his products out. “There are 20 countries where homoeopathy is illegal. We can break real boundaries [with the online system]”, he said.

Batra, who claims to have remedies for miscarriage and stammering, defended homoeopathy against its critics from the scientific establishment, saying that “everyone has a different personality so they have a different need. You will never get an agreement on what should be used. There are 200 medicines for a headache”.

Raekha Prasad
Book

A poignant memoir of grief and hope

Apollo, Dannie Abse reminds us in this hauntingly poignant memoir, was the god of poetry; but he was also the father of Aesculapius, the god of medicine. Both are therapeutic practices in their different ways, and between them they have moulded the life of this author, as both former chest specialist and distinguished poet. “Medicine”, Abse writes with his customary dry wit, “is my lawful wife and literature is my mistress. When I get tired of one I spend the night with the other”. He wears, he tells us, both the white and the purple coat: the former the garb of the physician, the latter the more exotic raiment of the artist.

Poetry and medicine, to be sure, occasionally collide. When Abse looks at portraits, he can find his aesthetic sense impaired by his physician’s eye for the pathological: “In the National Portrait Gallery, I have diagnosed jaundice (probably haemolitic), acme, profound anaemia, polycythaemia, thyrotoxicosis, and post-coital depression.” For the art-lover, a little knowledge can be a dangerous thing. Yet reason and emotion are not necessarily at odds. Poetry, Abse tells us in splendidly aphoristic style, “is written in the brain but the brain is bathed in blood”.

For all his weeping, however, this journal-keeper, as befits a physician, is rigorously unsentimental. (Sentimentality, he tells us in another fine poetic-cum-chemical image, “may sugar itself over and mush into the bacterial.”) He may “feel I’m lost in a foreign city and have to stop to read myself as if I were a map”; yet he has shed nothing of his Jewish sense of humour either. Abse’s uncle Isidore, asked what he did with his time, replied “Nothing. And I don’t do that until after lunch”. Abse’s son pointed to a row of his father’s books and announced proudly to a friend “Do you see those books over there? My Mum typed all of them.” Wit, as Oscar Wilde knew, is another way of transcending the unspeakable, stealing a march on misery.

Grief has no coherent shape, which is perhaps why this book is a dishevelled quiltwork of jokes, poems, anecdotes, aphorisms, literary reminiscences, political reflections, and snatches of lyrical Nature imagery. Memories of the vanished Joan are often subtly interwoven with the scent of flowers or the shifting of the seasons. In a curious way, her absence is acted out in the book, in the sense that most of the text is not directly about her. Like a friendly wraith, however, she keeps breaking insistently through Abse’s words like a “tearfully returning boomerang of grief”. The image beautifully captures the tedious, obsessive tenacity of this kind of sorrow, its neurotic compulsion to repeat.

Yet the writer’s words are also a way of keeping his slain partner at bay, displacing her as well as giving tongue to her. If the author is to delve inwards to deal with his loss, he must also turn outwards to re-engage once more with the world, think about football or the Iraq war or poetry readings or his native Wales. But because all this is at one level so much idle self-distraction, the eloquent silence that is Joan continually resounds through it, ruffling its edges and staining its shapes. She is the sound made by silence, just as the author himself feels absent from himself, leading a sort of posthumous existence. “There is the silence I have heard through my stethoscope”, Abse writes, “the silence between two heartbeats and the commanding silence when there is no heartbeat at all”.

Bereavement is a bundle of conflicting emotions, not a steady state. At times, Abse is chirpy enough to inform us that the great cellist Jacqueline Du Pré had a good line in filthy limericks; at other times he can manage no more than the stricken “We were a happy couple—more than one, less than two”. One hopes that he comes before long to share in the happiness this wise, funny, heart rending little book brings to its readers.

Terry Eagleton
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Lunch with The Lancet  Gill Samuels

A pharmaceutical industry stalwart isn’t the obvious choice for a leading role in a foundation that campaigns for health research for the poor. Over lunch in central London, Gill Samuels, who until 2 years ago headed science policy at Pfizer, confesses she herself was surprised and delighted by her recent appointment as Chair of the Foundation Council of the Global Forum for Health Research.

Her career looks outwardly corporate: a Shell postdoctoral toxicologist post, 7 years at ICI Pharmaceutical, and then Pfizer where she spent the next 27 years. But she has collaborated on projects outside of industry—the UK government commissions on human genetics and intellectual property rights, and working with WHO on global health. “Working in a corporation is not as limiting as people might think; they are not the great monoliths that they probably look like”, she says.

Being a female scientist can be limiting too, but Samuels insists she has never been aware of a glass ceiling. Her interest in science was instinctive and she took to early school science projects with gusto. Later, a desire to usefully apply science led her to health research. She is aware that for some people “science is a foreign country” with its own jargon. To make scientists more “user friendly”, she chairs the UK’s Cheltenham Festival of Science, which promotes science communication.

So how does this relate to health in poor countries? Well public pressure can influence government spending, but it requires direct engagement with science and technology. The Global Forum is now 10 years old, and Samuels will oversee the implementation of a new 10-year strategy. The plan will focus more heavily on health systems and infrastructure, resource flows, and managing research. Perhaps influenced by Samuels’ industry background, a buzz word for the strategy is “innovation”, not just in research but in challenging a “one size fits all” approach. While no-one could argue with the Forum’s aims, it is known for its conservative approach. Samuels wants the Forum to be more ambitious, “influencing the influencers”, rather than merely didactic and producing reports. Only the next few years will tell, but having Samuels at the helm may be no bad thing.

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In brief

Book On becoming a doctor
Most physicians, I would venture, remember the anatomy lab as their initiation into the fraternity of medicine. We receive an incomprehensible gift: the carte blanche for the human body; at the same time we run at the first hurdle of memorisation and regurgitation of minutiae, a process that will become so familiar during our training. Our cadavers are both human and not, dissections are both unimpressive and magical, academic and spiritual. We claim ownership of the body by naming it and the parts often threaten to take over our sense of the whole. When we recite those names and their anatomical relations with slight giddiness, are we communicating our wonder at the complexity of the body or merely our new sense of mastery? Our egos bound up with our scalpels and our exam grades, there are no easy answers.

Christine Montross, a poet and physician, purposefully or not, stumbles over these ambivalences with a gentle and abiding naivety in her first book, Body of Work. In a lyric sense, she inhabits the emotional space of the first-year medical student. “The cutting doesn’t feel awful or triumphant when I finish; it only feels done, and suddenly quiet”, she writes after her first lab, and it is in these poignant reflections that her poetry shines, simple and numinous. Of a brutal autopsy witnessed on a research rotation, “the horror is not what is present and cut apart but what has so completely and irreversibly gone”.

As the course progresses, the poetry of dissection is churned together with the stress of exams, the fear of inadequacy, and the difficulty of maintaining relationships, the hallmarks of the medical student’s life that Montross chronicles dutifully. She also intersperses expositions on the history of anatomy and these sections mark a shift from a lyrical voice to a more academic tone. If these sections and those others that seem a litany of body parts come off as pedantic, it is another instance of capturing the intended subject so intimately tied to the experience of anatomy. Just as medicine is caught between science and humanism, and anatomy is the most obvious metaphor for it, Montross’ small gem of a book is caught between memoir and exposition, its humility occasionally forced in its interlacing with erudition. Could it have been written any differently? If it were, it would not describe becoming a doctor so well.

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Ruben Sher

Former director of South Africa’s National AIDS Training and Outreach Programme. Born in Johannesburg on June 16, 1929, he died on Sept 10, 2007, of complications after heart surgery, aged 78 years.

Ruben Sher was widely dubbed the “grandfather of AIDS” in South Africa for being one of the first doctors in the country to identify the threat of the virus. With his white bushy beard, twinkling eyes, and sense of humour, he did indeed cut a grandfatherly figure. But his message—likening AIDS to a modern day Holocaust—was anything but that. “He saw the plague coming and warned of the need to take action. He was frustrated that nobody took him seriously”, said Francois Venter, of the Reproductive Health and HIV Research Unit at the University of Witwatersrand, Johannesburg. “The tragedy is that if we had intervened when we should have done, South Africa would be a very different place”, Venter told The Lancet. An estimated 5-4 million South Africans are infected with the virus, the highest total in the world.

Sher was born in Johannesburg to Jewish immigrant parents and studied medicine at the University of Witwatersrand. He first worked as a general practitioner and then joined the South African Institute for Medical Research as an immunologist and obtained his PhD in public health.

Sher’s involvement with HIV/AIDS started in 1982 when one of his sons fell ill. He took him for treatment to the USA and read in the newspapers about a mysterious new disease affecting members of the gay community. He visited the Centers for Disease Control and Prevention and met virologists there and became convinced that although HIV was unknown in South Africa it was probably already present. The next year he teamed up with Dennis Sifris to research the presence of HIV among homosexual men in Johannesburg. In the absence of an antibody test, Sher and Sifris looked for symptoms such as weight loss, specific opportunistic infections, and previous infections such as syphilis and hepatitis B. When an HIV test became available in 1985, they tested the blood samples they had collected and found that between 11-12% of the 200 men were already HIV positive.

Sher opened the country’s first HIV clinic in 1986. “A conservative old Jewish guy in a gay epidemic dealing with issues of gay sexuality and chilling with the gay community”, recalled Venter, who used to attend Sher’s lectures. Fearing that this could become an epidemic, Sher tried to sound the alarm bell. But his pleas for sex education and more action on prevention fell on deaf ears in the apartheid era. “We warned government. We warned corporations. We set up an AIDS advisory group...But everybody thought we were trying to threaten people”, Sher said in a 2006 interview with Health-E News, a medical news service. “The first case of AIDS in the black community was only detected in 1987…We were expecting it because we had immigrants here. We did a major study on the mines in 1986-87, which showed about 3.76% of Malawians working on the mines were positive. So, we’d anticipated there was going to be an epidemic...We alerted people...We had the evidence”, he told Health-E News.

Sher was bitterly disappointed that the African National Congress government, which came to power in 1994, also did too little to act against the virus. In the early years of the epidemic, Sher spent much time trying to dispel myths that the virus could be transmitted by casual physical contact. Des Martin a former president of the Southern African HIV Clinicians Society, said that Sher used to hug his patients. “He tried on an individual basis to dispel discrimination and show the people that he was someone who cared”, said Martin who worked closely with Sher.

Sher became the South African “face of AIDS” in terms of the medical and scientific response to the epidemic, Martin recalled. He rarely shied away from controversy and his forthright views made him a popular figure with journalists. He was also active in forging education and training links with overseas institutions. Sher was one of the founding fathers of the Southern African HIV Clinicians Society and later this month the Society will hold its inaugural annual Ruben Sher Memorial Lecture. From 1992 to 2002, Sher was a member of the board of directors of the AIDS Foundation of South Africa. Executive Director Debbie Mathew said that his experience and knowledge of HIV/AIDS proved invaluable. Sher is survived by his wife, three children, and one stepchild.

Clare Kapp
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Towards sustainable malaria control

Awash Teklehaimanot and co-authors (June 30, p 2143) claim that the social marketing of long-lasting insecticidal nets (LLINs) should be abandoned in favour of free distribution. Their argument fails to convince.

Their example of Ethiopia compares social marketing in the 1990s when only 1.5 million nets were supplied, with free distribution after 2005 when millions more were. They also compare social marketing of nets requiring the costs, logistics, and inconvenience of frequent retreatment with free handouts of those that do not (LLINs).

The purpose of social marketing is to use commercial distribution and sales mechanisms to access hard-to-reach areas: to the market stalls the poor have access to, not the formal health services that they do not. And although handouts can be assured of takers, the question remains of if and how they are used: LLINs also make very effective house curtains and covers for fish stalls, for example. They dismiss attempts to create “new markets for bednets that do not exist” as diverting funds from saving lives. But there was low demand for sexual and reproductive health products and services once, and social marketing and franchising have been very effective in raising that.

If the private distribution networks that cover Africa with tea, beer, and batteries are dismissed, what public network is to be put in place instead? Not government health services, certainly, which are failing to deliver even their current mandates. New fleets of UNDP trucks and planes, perhaps—that tried and tested way of diverting funds?

As Awash Teklehaimanot and colleagues claim in their Comment, antimalarial commodities such as bednets and drugs should ideally be available free of charge for mass distribution to affected communities. In reality, however, heavy reliance on free distribution cannot be sustainable in the fight against malaria.

Teklehaimanot and colleagues mention that comprehensive malaria control in Africa is achievable by 2010 with US$3 billion per year. However, this estimation is too optimistic. Its precondition “sound principles of public health and economics” will be extremely difficult to meet owing to the current political and economic situation in many African countries. Also, early diagnosis and treatment, indoor residual spraying, and the use of insecticide-treated nets are clearly becoming less effective with the rapid development and spread of resistance to drugs and insecticides.

We therefore argue that economically sustainable approaches, especially community-based actions, are crucial for successful malaria and vector control. While making antimalarial commodities available to affected communities, raising community awareness of the health and economical benefits of malaria prevention can promote their preventive actions. Additionally, environmental management for vector control with community participation would be cost effective, easy to apply, and can reduce the malaria risk ratio by as much as 88%.

Since malaria continues to be a major health threat worldwide, exploring and spreading sustainable control methods applicable to different parts of the world could eventually lead to containment of malaria. It might be slower than the free distribution approach, but it is much more promising.

We declare that we have no conflict of interest.

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Authors’ reply

Citing the Ethiopian example, Roger England attributes the low bednet distribution and uptake attained by social marketing from 1990 to 2004 to low supply. In fact, bednets targeted for social marketing were kept in store for extended periods, sometimes up to a year, owing to low demand. People were too poor to afford the subsidised nets even during epidemics.

The effectiveness of distribution and use is central to our paper, since free distribution of bednets has proved that not only do they reach intended...
users, but also that they will be adequately used and taken care of by those who receive them. In Tanzania, several years after nets were provided free of charge in rural areas, more than 90% were still in houses and brought in for annual retreatment.1

Social marketing reaches the least poor in urban households, but is unaffordable for the poorest people in African villages where the heaviest burden of malaria falls.2 The point is not to get some bednets into some remote location, which social marketing might accomplish. The goal is comprehensive coverage, including the bottom four-fifths of the income distribution. The Ethiopian programme secured funding from the Global Fund and other donors to reach universal coverage through free distribution of nets in rural villages. A steep rise in net coverage and equity over income groups occurred when Kenya moved from social marketing to reach universal coverage through free distribution of nets in rural areas, more than 90% were still in houses and brought free of charge in rural areas, more than 90% were still in houses and brought in for annual retreatment.1


We declare that we have no conflict of interest.

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Center for Global Health and Economic Development, The Earth Institute at Columbia University, New York, NY 10025, USA (AT, JS), and London School of Hygiene and Tropical Medicine, London, UK (CC)

Social marketing reaches the least poor in urban households, but is unaffordable for the poorest people in African villages where the heaviest burden of malaria falls.2 The point is not to get some bednets into some remote location, which social marketing might accomplish. The goal is comprehensive coverage, including the bottom four-fifths of the income distribution. The Ethiopian programme secured funding from the Global Fund and other donors to reach universal coverage through free distribution of nets in rural villages. A steep rise in net coverage and equity over income groups occurred when Kenya moved from social marketing to reach universal coverage through free distribution of nets in rural areas, more than 90% were still in houses and brought free of charge in rural areas, more than 90% were still in houses and brought in for annual retreatment.1


We declare that we have no conflict of interest.

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We declare that we have no conflict of interest.
data from slightly fewer women being analysed in the PARIS review than in the Cochrane review. The strength of our analysis was that the use of IPD enabled us to classify individual women more accurately as having received antiplatelets for primary prevention, and by whether they were high or low risk at trial entry, rather than having to include all women from one particular trial in an analysis as was necessary in the Cochrane aggregate data review.

Two factors might have contributed to the modest differences in data for fetal and neonatal deaths between the two reviews, as shown by M Chandiramani and colleagues. First, use of IPD allowed significant rechecking of the original data, which for some trials changed the overall result for this outcome. Second, the PARIS analyses used fetal or baby death before discharge as the definition of this outcome, rather than fetal or baby death at any time, as reported in the trials included in the Cochrane review. So, although the PARIS analysis included slightly fewer women, they had slightly more fetal or neonatal deaths. The net effect is a slight shift in both the relative risk and confidence interval. Nevertheless, the relative risks from both reviews are similar, both suggesting a modest reduction (10%) in the relative risk of baby death. Although the PARIS analysis gives a slightly more conservative estimate of benefit, which does not quite achieve significance, we believe it represents a worthwhile effect, especially when coupled with a clear reduction in the risk of preterm birth which is also an important outcome for mothers (and health-care systems).

Although it will be interesting to explore the differences between results of the PARIS and Cochrane reviews further, we believe they give the same overall message and we reiterate that we believe the PARIS review is the most reliable analysis of the effect of antiplatelets in preventing pre-eclampsia and the most robust data to discuss with women when making decisions about care.

We declare that we have no conflict of interest.

Lisa Askie, Lelila Duley, David Henderson-Smart, Lesley Stewart, on behalf of the PARIS Collaboration

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Two cochlear implants: halving the number of recipients

In their Comment (Sept 1, p 719),1 Benjamin Wei and colleagues deal with the issue of two cochlear implants and their superiority to one. Although the mentioned advantages are appreciated, in practice more important factors are involved in making the decision.

Most patients with hearing impairment live in developing countries with limited health-care budgets and where the rate of congenital deafness is higher than the 1–2 in 1000 rate of the developed world.2 The rate is estimated to be 2–3 per 1000 in Iran, yet in the past 10 years we have inserted fewer than 2000 cochlear implants. Most patients are from lower socioeconomic groups, there is no insurance coverage for cochlear implants, and the price of an implant is about US$20 000, which has not changed significantly since the mid-1990s. Luckily, almost all implants are distributed from the government sector so patients have to pay only a third of the price. However, this is still roughly equal to the gross domestic product per head.3 Although many families might describe the result as a miracle, use of two implants could only halve the number of recipients.

On the other hand, we have seen important changes in the design of the implants every 4–5 years.4 If a patient was given two implants 10 years ago, how could he be offered a newly designed hybrid implant now? Keeping in mind that, after insertion of conventional implants, we observe a gradual change in the normal structure of the cochlea, it seems unwise to hinder further therapeutic intervention for the patient with an eye to the advent of molecular and stem-cell technologies.

At present, use of two cochlear implants should be decided with more vigilance and a holistic view in most clinical settings.

We declare that we have no conflict of interest.

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Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial


Summary

Background Laser treatment for diabetic retinopathy is often associated with visual field reduction and other ocular side-effects. Our aim was to assess whether long-term lipid-lowering therapy with fenofibrate could reduce the progression of retinopathy and the need for laser treatment in patients with type 2 diabetes mellitus.

Methods The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a multinational randomised trial of 9795 patients aged 50–75 years with type 2 diabetes mellitus. Eligible patients were randomly assigned to receive fenofibrate 200 mg/day (n=4895) or matching placebo (n=4900). At each clinic visit, information concerning laser treatment for diabetic retinopathy—a prespecified tertiary endpoint of the main study—was gathered. Adjudication by ophthalmologists masked to treatment allocation defined instances of laser treatment for macular oedema, proliferative retinopathy, or other eye conditions. In a substudy of 1012 patients, standardised retinal photography was done and photographs graded with Early Treatment Diabetic Retinopathy Study (ETDRS) criteria to determine the cumulative incidence of diabetic retinopathy and its component lesions. Analyses were by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN64783481.

Findings Laser treatment was needed more frequently in participants with poorer glycaemic or blood pressure control than in those with good control of these factors, and in those with a greater burden of clinical microvascular disease, but the need for such treatment was not affected by plasma lipid concentrations. The requirement for first laser treatment for all retinopathy was significantly lower in the fenofibrate group than in the placebo group (164 [3·4%] patients on fenofibrate vs 238 [4·9%] on placebo; hazard ratio [HR] 0·69, 95% CI 0·56–0·84; p=0·0002; absolute risk reduction 1·5% [0·7–2·3%]). In the ophthalmology substudy, the primary endpoint of 2-step progression of retinopathy grade did not differ significantly between the two groups overall (46 [9·6%] patients on fenofibrate vs 57 [12·3%] on placebo; p=0·19) or in the subset of patients without pre-existing retinopathy (43 [11·4%] vs 43 [11·7%; p=0·87]). By contrast, in patients with pre-existing retinopathy, significantly fewer patients on fenofibrate had a 2-step progression than did those on placebo (three [3·1%] patients vs 14 [14·6%; p=0·004]. An exploratory composite endpoint of 2-step progression of retinopathy grade, macular oedema, or laser treatments was significantly lower in the fenofibrate group than in the placebo group (HR 0·66, 95% CI 0·47–0·94; p=0·022).

Interpretation Treatment with fenofibrate in individuals with type 2 diabetes mellitus reduces the need for laser treatment for diabetic retinopathy, although the mechanism of this effect does not seem to be related to plasma concentrations of lipids.

Introduction Diabetic retinopathy has become the leading cause of vision loss and blindness in working-age adults in both developed and developing countries. Visual loss results mainly from central macular oedema, and less frequently from proliferative diabetic retinopathy. The onset of diabetic retinopathy is characterised by vasodilation and hyperperfusion, followed by capillary loss and ischaemia. Leakage of protein and fluid from damaged capillaries leads to oedema at the macula, the focal centre of the retina, together with lipid and protein deposits termed hard exudates. The development of these pathological changes is strongly related to hyperglycaemia in type 2 diabetes. Laser treatment to photocoagulate ischaemic retina and leaking microaneurysms has been proven in clinical trials to slow or prevent further vision loss from diabetic retinopathy. Although successful, laser treatment is frequently associated with visual field reduction and other ocular side-effects, and so any treatment that could reduce the need for the use of lasers would be an important advance. Medical management of risk factors associated with diabetic retinopathy is also important in slowing the progression of retinal disease. Although there is clear evidence of an association between diabetic retinopathy and glycaemia, duration of diabetes, raised blood pressure, and microalbuminuria, neither control of glycaemia nor blood pressure has fully prevented the progression of diabetic retinopathy, underscoring the importance of also assessing the management of other potential risk factors. Raised serum cholesterol and triglyceride concentrations have been reported to be associated with both the...
development and severity of diabetic retinopathy. Increased lipid concentrations have also been linked in several studies to the development of macular oedema, or to hard exudate deposition or proliferative retinopathy. However, there is uncertainty regarding the beneficial effects of lipid lowering treatment for the management of diabetic retinopathy.

Nonetheless, the associations between raised lipid concentrations and the presence and severity of diabetic macular oedema and retinal hard exudate deposition highlight the potential for possible benefits from lipid-lowering drug therapy. Although statins have proven unsuccessful in preventing diabetic retinopathy, previous studies of peroxisome proliferator-activated receptor (PPAR)α agonists—also known as fibrates—in small numbers of patients have found beneficial effects on retinal and macular hard exudates.

The aim of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was to assess whether long-term lipid-lowering therapy with fenofibrate could reduce macrovascular and microvascular outcomes in type 2 diabetes. Previously, we found that, in patients with type 2 diabetes and adequate glycaemic and blood pressure control, there was a significant relative reduction of almost a third in the rate of first laser treatment events for retinopathy after an average of 5 years treatment with fenofibrate 200 mg a day. Here, we report in detail on the effects of fenofibrate therapy on ophthalmic complications, and attempt to identify the underlying pathologies being treated in patients receiving laser treatment.

Methods

Patients

Participants in FIELD have been described in detail elsewhere. Briefly, individuals were eligible for inclusion if they were aged between 50 and 75 years, had type 2 diabetes according to WHO criteria, and had an initial plasma total cholesterol concentration of 3–6.5 mmol/L and a total cholesterol/HDL-cholesterol ratio of 4–0 or more, or a plasma triglyceride concentration of 1–5 mmol/L, without requiring lipid-modifying treatment at study entry. Individuals with significant renal impairment (plasma creatinine >130 µmol/L), chronic liver disease, or symptomatic gallbladder disease, or who had experienced a cardiovascular event within the 3 months before recruitment were excluded.

All patients provided written informed consent and the study protocol was approved by local and national ethics committees in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Procedures

9795 patients were eligible for inclusion, and were randomly assigned to receive micronised fenofibrate 200 mg once daily (Laboratoires Fournier, Dijon, France)
instances of laser photocoagulation therapy for diabetic retinopathy were then recorded routinely at every follow-up visit, and supporting documentation was requested subsequently. The occurrence of laser treatment for retinopathy was a prespecified tertiary endpoint of the main FIELD study. There were no constraints in the study protocol, however, regarding the use of laser treatment for diabetic retinopathy in trial participants, which remained at the discretion of each participant’s usual doctors. As such, use of laser treatment in the FIELD study reflects current clinical practice, and would not be expected to have differed systematically between groups.

Documentation regarding the use of laser treatment was adjudicated, masked to treatment allocation, by at least two ophthalmologists involved in the FIELD study (PM, PAS) to ascertain the reason for each episode of laser treatment. New laser treatment events were recorded when the date of laser treatment was at least 10 weeks after the previously reported course of treatment. All instances of laser treatment were classified as either laser treatment for macular oedema, or for proliferative retinopathy without macular involvement. Where involvement of the macula as the underlying pathology could not be reliably determined from supporting documentation (87 cases only), these cases were classified as laser treatment for proliferative retinopathy without macular involvement. Participants in whom laser treatment was identified as being for treatment of capsular opacity, iridotomy, retinal breaks, or for other non-diabetic conditions, were excluded from the analysis.

At 22 of 63 FIELD sites, patients were also approached to participate in an ophthalmology substudy involving serial retinal photography. Consenting patients were eligible provided that two-field colour fundus photographs of both eyes showed no evidence of proliferative retinopathy, severe non-proliferative retinopathy, clinically significant macular oedema, or indication for, or evidence of a history of laser treatment at a screening examination done during the placebo run-in phase. A number of other ocular pathologies or technical problems also rendered patients ineligible.

Retinopathy status and severity were assessed from two-field 45° colour fundus photographs of the macula (stereoscopic) and a disc/nasal field taken at the baseline, 2 year, 5 year, and end of study examinations as part of the FIELD follow-up, to look for long-term changes and possible effects of treatment. Grading of retinopathy and macular oedema was done by the study ophthalmologists (PM, PAS), or a trained photographic grader (MSM), who were masked to treatment allocation, in accordance with adapted Early Treatment Diabetes Retinopathy Study (ETDRS) criteria, from grade 10 to 99 (webtable 1).5,12

Before retinal photography, pupils were dilated with 1% tropicamide, which was repeated to achieve adequate pupil dilation (at least 6 mm in diameter). Colour retinal

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### Table 1: Number of laser treatment courses per patient during follow-up and cumulative totals by allocated treatment group

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=4900)</th>
<th>Fenofibrate (n=4895)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>Number of treatments</td>
<td>Number of patients (%)</td>
</tr>
<tr>
<td>0</td>
<td>4662 (95%)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>121 (2%)</td>
<td>121</td>
</tr>
<tr>
<td>2</td>
<td>48 (1%)</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>27 (0.6%)</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>15 (0.3%)</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>10 (0.2%)</td>
<td>50</td>
</tr>
<tr>
<td>6-12</td>
<td>17 (0.3%)</td>
<td>127</td>
</tr>
<tr>
<td>Cumulative total</td>
<td>234 (5%)</td>
<td>535</td>
</tr>
</tbody>
</table>

*p = 0.0003 for difference in incidence density rates by treatment assignment (Poisson test).

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### Patient characteristics

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>Placebo (n=4900)</th>
<th>Fenofibrate (n=4895)</th>
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<tbody>
<tr>
<td>Sex (male)</td>
<td>3864 (78.6%)</td>
<td>3748 (77%)</td>
</tr>
<tr>
<td>Ethnic origin (white)</td>
<td>8728 (92.9%)</td>
<td>8636 (92.3%)</td>
</tr>
<tr>
<td>Age at visit 1 years</td>
<td>63.3 (6.9)</td>
<td>63.8 (6.7)</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>5.0 (2.9–9.0)</td>
<td>5.0 (2.9–9.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.6 (6.8–33.5)</td>
<td>28.6 (6.8–33.5)</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.94 (0.88–1.00)</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>140.3 (15.3)</td>
<td>140.9 (15.3)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>82.0 (8.5)</td>
<td>82.0 (8.5)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>892 (9.5%)</td>
<td>892 (9.5%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>4747 (50.5%)</td>
<td>4747 (50.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical history</th>
<th>Placebo (n=4900)</th>
<th>Fenofibrate (n=4895)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous cardiovascular disease</td>
<td>2036 (21.7%)</td>
<td>95 (23.6%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>466 (5.0%)</td>
<td>194 (4.7%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>324 (3.4%)</td>
<td>234 (5.7%)</td>
</tr>
<tr>
<td>Angina</td>
<td>1136 (12.1%)</td>
<td>512 (12.7%)</td>
</tr>
<tr>
<td>Periperal vascular disease</td>
<td>670 (7.1%)</td>
<td>420 (10.4%)</td>
</tr>
<tr>
<td>Coronary revascularisation (CABG or PTCA)</td>
<td>348 (3.7%)</td>
<td>154 (3.7%)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>529 (5.6%)</td>
<td>217 (5.4%)</td>
</tr>
<tr>
<td>Any microvascular disease</td>
<td>1787 (18.8%)</td>
<td>159 (4.5%)</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>614 (6.5%)</td>
<td>200 (4.9%)</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>1239 (13.1%)</td>
<td>357 (9.1%)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>243 (2.6%)</td>
<td>36 (0.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory data</th>
<th>Placebo (n=4900)</th>
<th>Fenofibrate (n=4895)</th>
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</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.04 (4.70)</td>
<td>5.04 (4.70)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.07 (0.65)</td>
<td>3.07 (0.65)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.10 (0.26)</td>
<td>1.10 (0.26)</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.74 (1.34–2.33)</td>
<td>1.71 (1.33–2.27)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>8.4 (7.0–10.2)</td>
<td>8.4 (7.0–10.2)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.8 (6.1–7.7)</td>
<td>6.8 (6.1–7.7)</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>77 (65.8)</td>
<td>77 (65.8)</td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>9.5 (8.0–11.5)</td>
<td>10.1 (8.3–12.4)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>3569 (38.0%)</td>
<td>141 (35.1%)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>1277 (18.4%)</td>
<td>1277 (18.4%)</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>257 (2.7%)</td>
<td>257 (2.7%)</td>
</tr>
</tbody>
</table>

(Continues on next page)
Table 2: Baseline characteristics of participants requiring or not requiring laser treatment during the study

<table>
<thead>
<tr>
<th>Baseline cardiovascular medication</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Antithrombotic</td>
<td>2923 (31.1%)</td>
<td>145 (16.1%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>2695 (28.7%)</td>
<td>134 (33.3%)</td>
</tr>
<tr>
<td>Antithrombotic (excluding aspirin)</td>
<td>292 (3.1%)</td>
<td>16 (4.0%)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>3127 (33.3%)</td>
<td>154 (38.3%)</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonist</td>
<td>504 (5.4%)</td>
<td>18 (4.5%)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>1368 (14.6%)</td>
<td>54 (13.4%)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>1813 (19.3%)</td>
<td>79 (19.7%)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>525 (5.6%)</td>
<td>25 (6.2%)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>1424 (15.2%)</td>
<td>61 (15.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline blood-glucose-lowering medication</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet alone</td>
<td>2602 (28.1%)</td>
<td>6 (1.7%)</td>
</tr>
<tr>
<td>Metformin alone</td>
<td>1699 (18.1%)</td>
<td>22 (5.5%)</td>
</tr>
<tr>
<td>Sulfonylurea alone</td>
<td>1568 (16.7%)</td>
<td>43 (10.7%)</td>
</tr>
<tr>
<td>Metformin + sulfonylurea</td>
<td>2173 (23.1%)</td>
<td>147 (36.6%)</td>
</tr>
<tr>
<td>Other oral agent</td>
<td>19 (0.2%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Metformin and/or sulfonylurea + other agent</td>
<td>155 (1.7%)</td>
<td>15 (3.7%)</td>
</tr>
<tr>
<td>Insulin alone</td>
<td>529 (5.6%)</td>
<td>78 (19.4%)</td>
</tr>
<tr>
<td>Insulin + oral agent</td>
<td>648 (6.9%)</td>
<td>91 (22.6%)</td>
</tr>
</tbody>
</table>

Data are n (%), mean (SD), or median (IQR). BMI=body-mass index. CABG=coronary artery bypass graft surgery. PTA=percutaneous transluminal coronary angioplasty.

(Continued from previous page)

Statistical analysis

All analyses were done on an intention-to-treat basis. Treatment differences for baseline characteristics were analysed with χ² tests for categorical variables, t tests for continuous variables, or if the distribution of the data was non-normal, the Wilcoxon rank-sum test. Cox proportional hazards analysis was used to compute hazard ratios (HR) and 95% CI to assess the effect of fenofibrate treatment on the time to first laser treatment event. Where appropriate, p values were computed with the log-rank test. Cumulative incidence curves of the time to first laser treatment event according to the main underlying cause, and by treatment group, were calculated with the Kaplan-Meier method. For multiple event analysis, a Poisson model on the number of laser treatment courses was used. The Poisson analysis yields an incidence density ratio (analogous to the HR), reflecting the relative change in event rate per unit time (per month in this case) for the fenofibrate group relative to the placebo group. For the substudy, in all participants, the most severely affected eye at baseline was used for the analysis, but photographs of both eyes were graded. In cases of equal severity at baseline, the values for the right eye were used. For low-count events, the conditional binomial exact test was used. For analyses including outcomes measured at intervals, interval-censored proportional hazards methods were used. All statistical inferences were drawn with a two-sided p value of 0.05. All statistical analyses were done with SAS version 9.1 or ACCoRD (Analysis of Censored and Correlated Data).

See Online for webtable 2

Photographs were taken of two fields in both eyes according to guidelines of the EURODIAB study by using a suitable retinal camera.19 The macular field was imaged so that the optic disc was at the nasal end of the field. The disc/nasal field was imaged with the optic disc positioned one disc-diameter from the temporal edge of the field. A single photograph of any other significant retinal pathology was also taken. Existing fundus cameras at different sites were used so that there was some variability in the photographic angle taken; however, the camera did not differ between treatment groups at any site. All but two sites provided photographs in a non-digital format. After film processing, the slides were analysed at either of the two grading centres in Australia and Finland (from baseline to study end) and the grading of 100 patients was cross-checked between the grading sites for quality assessment and concordance, which were high (weighted κ values were 0.74 for grade of diabetic retinopathy, 1.0 for presence of macular oedema).

Macular oedema was characterised by the presence of thickening of the retina. Clinically significant macular oedema was defined as having one of the three following criteria: retinal thickening at or within 500 µm of the centre of the macula; hard exudates at or within 500 µm of the centre of the macula associated with macular oedema; and zone(s) of retinal thickening at least one disc area in size, any part of which is within one disc diameter of the centre of the macula.17 Macular oedema was graded according to whether it was absent, present but not clinically significant (not involving the foveal centre), or present and clinically significant (involving the foveal centre). Hard exudates were graded as absent or present and, when present, were graded by comparison with standard photographs by use of the hard exudate scale of the modified ETDRS system (webtable 2).21

The main objective of the substudy was to assess the effects of treatment on progression of diabetic retinopathy. This was defined as at least a 2-step increase in ETDRS grade (webtable 1) after 2 years or more of follow-up for all patients, and was also subclassified as (1) secondary (2-step progression of existing retinopathy in those with a baseline grade of 20 or more) and (2) primary (2-step progression to retinopathy in those with a baseline grade of 15 or less). Secondary endpoints included one-step progression, the occurrence or progression of macular oedema, of hard exudates, and the occurrence of laser treatment, vitrectomy surgery, and cataract (including surgery), and deterioration of visual acuity by two lines (Snellen chart). In the substudy, the development of new retinopathy was defined as grade 20 or greater in the ETDRS classification after 2 years or more of follow-up in patients with grade 15 or less at baseline. A post-hoc exploratory composite endpoint reflecting the development of significant retinal pathology included any of a 2-step progression of retinopathy grade, new macular oedema, or laser treatment.
The FIELD study is registered as an International Standard Randomised Controlled Trial, number ISRCTN64783481.

Role of the funding source
The study was designed by an independent management committee and an ophthalmology working group, and was coordinated by the National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Australia. Two non-voting representatives of the main sponsor attended meetings of the management committee. The sponsor of the study had no role in data collection or data analysis. The writing committee had full access to all the data in the study. The writing committee and study management committee had final responsibility for the decision to submit for publication.

Results
Of the 9795 participants randomised into the FIELD study, 4895 were assigned to receive fenofibrate and 4900 were assigned to receive matching placebo. 8.3% (412 participants in the placebo group and 402 in the fenofibrate group) of patients self-reported a history of diagnosed retinopathy before study entry, and 91.7% (4488 of those allocated placebo and 4493 allocated fenofibrate) reported no history of retinopathy. The fenofibrate and placebo treatment groups were well matched in terms of baseline characteristics, as reported previously. Follow-up for any instances of laser treatment for retinopathy was complete to the end of study for over 99% of the patients who were still alive (figure 1).

402 (4.1%) of patients underwent laser treatment for diabetic retinopathy during follow-up. Almost half of all patients receiving on-study laser treatment required several courses of therapy (total of 872 courses, range 2–12 courses per patient; table 1). The baseline characteristics and medications of those who went on to require or not require laser treatment were strikingly different (table 2). Patients receiving laser treatment during the study were more likely to be male, had a 7-year longer average duration of diabetes, a marginally higher waist-hip ratio, around a 5 mm Hg higher average systolic blood pressure, and were more likely to have had a stroke or peripheral vascular disease than were those who did not require laser treatment. They were also more likely to have reported prior microvascular complications, including retinopathy, neuropathy, and nephropathy at baseline. Furthermore, fasting plasma glucose concentrations and HbA1c levels were higher in patients needing laser treatment than in those who did not need it (table 2), despite more aggressive therapy for their diabetes. Homocysteine levels were significantly higher in patients needing laser treatment; such patients were also more likely to have measured microalbuminuria or macroalbuminuria. No differences were seen in baseline concentrations of blood lipids, including total cholesterol, HDL cholesterol, calculated LDL cholesterol, or triglycerides. Participants receiving laser treatment were significantly more likely at baseline to have been prescribed antithrombotic medication (mainly aspirin), and angiotensin-converting enzyme (ACE) inhibitors, and non-dietary blood glucose-lowering therapies (mainly metformin, sulfonylureas, or insulin) than were those not needing laser treatment (table 2), reflecting their longer diabetes duration, worse glycaemic control, and consequently greater prevalence of vascular complications. At the end of the study, use of these treatments was even higher in patients receiving laser treatment, particularly the use of insulin therapy (webtable 3).

See Online for webtable 3

Figure 2: Cumulative risk curves of time to event of any first laser treatment, by treatment group
Macular oedema indicates laser treatment where the macula was involved; proliferative retinopathy shows cases without macular involvement; all retinopathy includes all first instances of laser treatment for any diabetic retinopathy.
Figure 3: Effect of fenofibrate on first and all laser treatment events
Counts for each underlying pathology are shown; for all events, a patient was counted only once under each type of pathology.
*Without macular involvement.

Table 3: Stage of diabetic retinopathy (ETDRS grading) at baseline of the worse eye in patients needing laser treatment

<table>
<thead>
<tr>
<th>ETDRS grading</th>
<th>Placebo: number needing laser treatment/number in group (%)</th>
<th>Fenofibrate: number needing laser treatment/number in group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>10/357 (0.28%)</td>
<td>1/363 (0.28%)</td>
</tr>
<tr>
<td>Questionable</td>
<td>14/40 (2.5%)</td>
<td>0/44 (0%)</td>
</tr>
<tr>
<td>Minimal, non-proliferative</td>
<td>20/352 (5.8%)</td>
<td>0/41 (0%)</td>
</tr>
<tr>
<td>Mild, non-proliferative</td>
<td>35/426 (15.3%)</td>
<td>2/47 (4.3%)</td>
</tr>
<tr>
<td>Moderate, non-proliferative</td>
<td>43/721 (47.6%)</td>
<td>1/14 (7.1%)</td>
</tr>
<tr>
<td>Moderately severe non-proliferative or worse</td>
<td>47-99/44 (100%)</td>
<td>1/3 (33.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>23/500 (4.6%)</td>
<td>5/512 (1.0%)</td>
</tr>
</tbody>
</table>

*Each percentage expresses the number of patients needing laser treatment as a proportion of the total number with that Early Treatment Diabetic Retinopathy Study (ETDRS) grade of retinopathy at baseline. Focussed analysis: fewer first instances of laser treatment in those allocated to fenofibrate than in those allocated to placebo, p=0.0004.

The relative effects of fenofibrate seemed to be larger in those without (39% reduction, 95% CI 18–54; p=0.0008) than in those with (23% reduction, −1 to 42; p=0.06) a history of retinopathy, although the difference was not statistically significant (p value for heterogeneity 0.30; figure 3). The risk of first laser treatment in the placebo group over an average of 5 years was about 3% in those without a history of retinopathy and 27% in those with such a history (figure 3); consequently, the absolute risk reduction was much larger in patients with a history of retinopathy: if treated with fenofibrate, there would be 5.8 fewer first laser treatments per 100 patients (number needed to treat [NNT] 17) in those with a history of retinopathy compared with 1.1 fewer treatments per 100 patients treated with placebo (NNT 90) in those without a history of retinopathy.

Of the 872 total courses of laser treatment, 535 were given to 238 (4.9%) patients on placebo, and 337 to 164 (3.4%) patients on fenofibrate (relative reduction with fenofibrate 37%; 95% CI 19–51; p=0.0003; figure 3). There was a relative reduction in the need for laser treatment of 36% (95% CI 14–52; p=0.003) with fenofibrate treatment in those with any maculopathy, and of 38% (11–57; p=0.009) in those with proliferative retinopathy (figure 3). Although the relative effects of fenofibrate seemed to be larger in those without (49% reduction, 95% CI 27–64; p=0.0002) than in those with (24% reduction, −5 to 45; p=0.10) a history of retinopathy, these differences were not statistically significant (p value for heterogeneity 0.1). These differences represent an average of 2.8 fewer events per 100 patients treated with fenofibrate over 5 years without a history of retinopathy, compared with 16.2 fewer events per 100 patients treated with fenofibrate over 5 years with a history of retinopathy.

The safety profiles of fenofibrate and matching placebo were much the same over an average of 5 years follow-up, with small increases seen only in the rare clinical events of pancreatitis and pulmonary embolism. Increases in both plasma creatinine (average around 15% at 1 year) and plasma homocysteine (average around 41% at 1 year)

465 of the 872 courses of laser treatment done during the FIELD study were first laser treatments deemed to be for macular oedema or proliferative retinopathy. Most of these first laser treatments were for macular oedema alone or associated with proliferative retinopathy (282; 61% of first treatments), with the remainder (183; 39%) being for proliferative retinopathy without macular involvement. Baseline lipid concentrations did not differ between those whose first laser treatment was given for macular oedema compared with proliferative retinopathy (data not shown).

The requirement for first laser treatment for any retinopathy was significantly lower in the fenofibrate group than in the placebo group (238 [4.9%] patients in the placebo group vs 164 [3.4%] patients in the fenofibrate group; HR 0.69, 95% CI 0.56–0.84; p=0.0002), corresponding to an absolute risk reduction of 1.5% (0.7–2.3). There were similar estimated relative reductions in the number of patients needing first laser treatment for any maculopathy (31% reduction with fenofibrate, 95% CI 13–46; p=0.002) and in those needing such treatment for proliferative retinopathy (30% reduction with fenofibrate, 7–48; p=0.015), corresponding to absolute risk reductions of 1.1% (0.4–1.7) and 0.7% (0.1–1.2), respectively (figure 2 and figure 3). These effect sizes remained almost identical after adjustment for the main baseline characteristics predicting the need for laser treatment (data not shown). For each pathology, visible separation of the cumulative incidence curves emerged within 8 months of starting fenofibrate treatment, with progressively greater benefits accumulating over time (figure 2).

The relative effects of fenofibrate seemed to be larger in those without (39% reduction, 95% CI 18–54; p=0.0008) than in those with (23% reduction, −1 to 42; p=0.06) a history of retinopathy, although the difference was not statistically significant (p value for heterogeneity 0.30; figure 3). The risk of first laser treatment in the placebo group over an average of 5 years was about 3% in those without a history of retinopathy and 27% in those with such a history (figure 3); consequently, the absolute risk reduction was much larger in patients with a history of retinopathy: if treated with fenofibrate, there would be 5.8 fewer first laser treatments per 100 patients (number needed to treat [NNT] 17) in those with a history of retinopathy compared with 1.1 fewer treatments per 100 patients treated with placebo (NNT 90) in those without a history of retinopathy.

Of the 872 total courses of laser treatment, 535 were given to 238 (4.9%) patients on placebo, and 337 to 164 (3.4%) patients on fenofibrate (relative reduction with fenofibrate 37%; 95% CI 19–51; p=0.0003; figure 3). There was a relative reduction in the need for laser treatment of 36% (95% CI 14–52; p=0.003) with fenofibrate treatment in those with any maculopathy, and of 38% (11–57; p=0.009) in those with proliferative retinopathy (figure 3). Although the relative effects of fenofibrate seemed to be larger in those without (49% reduction, 95% CI 27–64; p=0.0002) than in those with (24% reduction, −5 to 45; p=0.10) a history of retinopathy, these differences were not statistically significant (p value for heterogeneity 0.1). These differences represent an average of 2.8 fewer events per 100 patients treated with fenofibrate over 5 years without a history of retinopathy, compared with 16.2 fewer events per 100 patients treated with fenofibrate over 5 years with a history of retinopathy.

The safety profiles of fenofibrate and matching placebo were much the same over an average of 5 years follow-up, with small increases seen only in the rare clinical events of pancreatitis and pulmonary embolism. Increases in both plasma creatinine (average around 15% at 1 year) and plasma homocysteine (average around 41% at 1 year)
concentrations were seen soon after the commencement of active treatment, but levels of both were found to reverse over 6–8 weeks after drug withdrawal at the end of the study.10

1012 (10.3% of the whole study population) participants, recruited from 22 participating study centres, further consented to, and were eligible for participation in, the ophthalmology substudy. Patients who were recruited to the substudy were much the same as those not participating (data not shown), including in terms of baseline concentrations of blood lipids. Participants had a slightly lower rate of previous cardiovascular disease (16% vs 22%), and less history of retinopathy (4.5% vs 8.7%) compared with those who did not participate in the substudy. Of the participants in the substudy, 850 (84%; 421 allocated to placebo, 429 allocated to fenofibrate) were followed up with detailed eye examinations to the end of the study (figure 1). 127 (12.5%) patients were missing end of study follow-up data, including 67 (6-6%) with no data for any point during follow-up in the substudy.

Of the 1012 patients recruited into the substudy, around 80% had no or questionable diabetes-related retinopathy at baseline (ETDRS grades 10, 14, or 15), and a low risk for subsequent laser treatment (<3%; table 3). ETDRS scores at baseline were well balanced between the two groups (table 3). The risk of needing laser treatment increased with increasing baseline ETDRS grades of retinopathy (table 3 and figure 4). 28 patients in the substudy required a first laser intervention for diabetic eye disease; most of whom had minimal to moderately severe non-proliferative diabetic retinopathy (ETDRS grades 20–47). The use of drug treatments, including antihypertensives, antidiabetic therapy, and statins, was either similar or greater in participants on placebo than in those on fenofibrate by the end of the study (webtable 4).

The primary endpoint of 2-step progression of retinopathy grade did not differ significantly between the two groups (table 4). However, in patients with pre-existing retinopathy, significantly fewer patients on fenofibrate had a 2-step progression than did those on placebo (three [3·1%] patients on fenofibrate vs 14 [4.6%] on placebo; p=0·004). By contrast, the number of patients without pre-existing retinopathy who had a 2-step progression was much the same in the two groups (43 [11.7%] vs 47 [12.1%]; p=0·9). The treatment effect within these two main subgroups differed significantly (test for interaction p=0·019).

23 patients in the placebo group and five in the fenofibrate group received one or more laser treatments over the course of the study (HR 0·21, 95% CI 0·08–0·54; p=0·0004; table 3 and figure 4). The occurrence of new retinopathy was not reduced by fenofibrate, nor was the occurrence or progression of hard exudates (table 4). Worsening in visual acuity did not differ significantly between groups (table 4), nor did numbers showing equivalent improvement. There were fewer instances of macular oedema in those treated with fenofibrate than in those on placebo (p=0·09). The risk of the composite endpoint of any of 2-step progression of retinopathy grade, development of macular oedema, or one or more laser treatments (either eye) was significantly lower in the fenofibrate group than in the placebo group (HR 0·66, 95% CI 0·47–0·94; p=0·022; table 4).

**Table 4: Main outcomes for the ophthalmology substudy**

<table>
<thead>
<tr>
<th>Intercurrent events</th>
<th>Placebo group (n=500)</th>
<th>Fenofibrate group (n=512)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser treatment (one or more) for diabetic retinopathy</td>
<td>22 (4·6%)</td>
<td>5 (1·0%)</td>
<td>0·0004</td>
</tr>
<tr>
<td>Vitrectomy surgery</td>
<td>1 (0·2%)</td>
<td>2 (0·4%)</td>
<td>0·73</td>
</tr>
<tr>
<td>Cataract or cataract surgery</td>
<td>22 (5·6%)</td>
<td>37 (7·2%)</td>
<td>0·29</td>
</tr>
<tr>
<td>2-step progression of retinopathy (primary endpoint)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>57 (12·3%)</td>
<td>46 (9·6%)</td>
<td>0·19</td>
</tr>
<tr>
<td>No pre-existing retinopathy</td>
<td>43 (11·7%)</td>
<td>43 (11·4%)</td>
<td>0·87*</td>
</tr>
<tr>
<td>Pre-existing retinopathy</td>
<td>14 (14·6%)</td>
<td>3 (3·1%)</td>
<td>0·004*</td>
</tr>
<tr>
<td>Other outcomes diagnosed at scheduled eye visits (2 years, 5 years, study end)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-step progression of retinopathy grade</td>
<td>106 (22·9%)</td>
<td>104 (21·8%)</td>
<td>0·69</td>
</tr>
<tr>
<td>Occurrence of new retinopathy</td>
<td>45 (12·3%)</td>
<td>46 (12·1%)</td>
<td>0·96</td>
</tr>
<tr>
<td>Occurrence of new hard exudates</td>
<td>14 (3·1%)</td>
<td>16 (3·5%)</td>
<td>0·78</td>
</tr>
<tr>
<td>Any progression of hard exudates</td>
<td>2 (14·3%)</td>
<td>2 (13·3%)</td>
<td>0·99</td>
</tr>
<tr>
<td>2-line worsening in visual acuity (Snellen chart)</td>
<td>90 (29·1%)</td>
<td>97 (30·7%)</td>
<td>0·67</td>
</tr>
<tr>
<td>Occurrence of any macular oedema</td>
<td>10 (2·2%)</td>
<td>4 (0·8%)</td>
<td>0·09</td>
</tr>
<tr>
<td>Composite outcome of significant retinal pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any of 2-step progression of retinopathy grade, macular oedema, or laser treatment (either eye)</td>
<td>75 (16·1%)</td>
<td>53 (11·1%)</td>
<td>0·022</td>
</tr>
</tbody>
</table>

* p value for interaction between treatment effects in those with and without pre-existing retinopathy. See Online for webtable 4.
Discussion

Our results show that treatment with micronised fenofibrate—in addition to therapies for hyperglycaemia and other risk factors for retinopathy—reduces the need for laser treatment for diabetic retinopathy in individuals with type 2 diabetes. This reduction was mainly associated with a lower prevalence of macular oedema as the underlying cause of diabetic retinopathy, although the need for treatment for proliferative retinopathy without macular involvement was also reduced by a similar amount. These findings are supported by less progression of pre-existing retinopathy with fenofibrate and the suggestion of less macular oedema in the ophthalmology substudy, in which the frequency of the exploratory composite endpoint of progression, macular oedema, or laser treatment was about a third lower in the fenofibrate group relative to the placebo group. Of interest is that the benefit of treatment in the substudy was largely seen in patients with pre-existing retinopathy and that there was not a significant reduction in 2-step progression of retinopathy grade in patients without pre-existing disease. No differences were seen in the substudy in terms of deterioration in visual acuity, or the development or progression of hard exudates, but those eligible for the substudy were a low-risk sample, offering limited power to explore these outcomes, and the numbers of all events in the substudy were small.

A somewhat greater reduction in the relative risk of laser treatment was seen when all laser treatment events were assessed, suggesting that there is a continuing benefit beyond the first treatment. Perhaps most striking was the apparent rapid onset of benefit of fenofibrate therapy, with divergence in the need for laser treatment evident within about 8 months of treatment allocation. Although the reduction in the relative risk of laser treatment with fenofibrate seemed to be more pronounced in patients without a history of diabetic eye disease, this might have been due to previously undiagnosed retinopathy in many of these patients subsequently undergoing laser treatment. Further, the estimated absolute risk reduction was much larger in patients with a history of diabetic eye disease.

The actual mode(s) of action of fenofibrate responsible for achieving these reported benefits are unclear. Fenofibrate is a lipid-modifying agent, and after 4 months of treatment had reduced total cholesterol concentrations by 11%, LDL-cholesterol concentrations by 12%, and triglyceride concentrations by 29%, and had increased HDL-cholesterol concentrations by 5%. However, the effect on individual lipid parameters was attenuated over the course of the study, and there was no clinically important difference in HDL-cholesterol concentrations at study completion between the two groups.

Additionally, none of these lipid concentrations at baseline seemed to affect the likelihood of developing retinopathy requiring laser treatment, despite small trials of both fibrates and statins suggesting improvements in ocular findings. Nonetheless, it is possible that intraretinal lipid transport rather than serum lipid concentrations might be more important in the pathogenesis of diabetic retinopathy.

Even though the requirement over 5 years for laser treatment was strongly associated with higher baseline concentrations of fasting glucose and of HbA1c, fenofibrate did not reduce either of these markers of diabetes control. Neither did fenofibrate lower systolic blood pressure, also strongly associated with laser requirement, by as much (average <2 mm Hg lower than with placebo) as reported in the ADVANCE trial of perindopril plus indapamide in diabetes (decrease of 5·6 mm Hg), in which reductions in eye events were not statistically significant. Furthermore, the benefits observed in the FIELD study were achieved against a background of medical care that, by the end of the study, included the use of ACE inhibitors or angiotensin II receptor blockers in more than 60% of patients in both groups, with all antihypertensive drug classes being more commonly used over time in the placebo group than in the fenofibrate group. Additionally, significantly more statin use occurred in the placebo than fenofibrate group over time.

These findings suggest that the mechanisms of benefit of fenofibrate in diabetic retinopathy must go beyond the effects of this drug on lipid concentrations or to lower blood pressure, and might be conferred mainly by other means. If so, this could indicate a mechanism of action that operates even when lipid concentrations have been controlled effectively by statin therapy and blood pressure by antihypertensive treatment.

Progressive microvascular ischaemia with vascular leak occurring within the ischaemic retina or, in more severe cases, new vessel proliferation and its sequelae, are the main features of diabetic retinopathy. Macular oedema, however, is the most frequent cause of both threatened and actual visual loss. The mechanisms by which fenofibrate might improve microvascular outcomes are yet to be fully elucidated. PPARα agonists are reported to inhibit the vascular endothelial growth factor (VEGF) pathway important in angiogenesis, inflammation, and cell migration, all thought to have a role in the progression of diabetic retinopathy. Fenofibrate has been shown to regulate retinal endothelial cell survival and to prevent apoptotic cell death. The drug has also been shown to stimulate expression of VEGF mRNA in the retina via the AMP-activated protein kinase (AMPK) signal transduction pathway. VEGF may be increased early in the course of diabetic retinopathy as a mechanism to maintain the integrity of the endothelial vascular bed.

Fenofibrate has also been shown to improve endothelial-dependent vascular reactivity. Together, these studies suggest that fenofibrate might prevent the need for laser treatment in diabetic retinopathy by inhibiting apoptosis of retinal endothelial cells, preventing...
cellular migration, and reducing local inflammatory processes, with implications for pathological processes such as retinal capillary leakage.

There have been suggestions that inflammation might be involved in the progression of diabetic retinopathy. The concentration of the RANTES cytokine is raised in individuals with severe non-proliferative diabetic retinopathy, compared with those with less severe non-proliferative retinopathy. Furthermore, monocyte chemoattractant protein 1 (MCP1) and intercellular adhesion molecule 1 (ICAM1) are upregulated within the retinal tissue in advanced diabetic retinopathy. In hepatocytes, fenofibrate was shown to inhibit protein production induced by tumour necrosis factor alpha (TNFα) and mRNA expression of RANTES. In a double-blind controlled clinical trial of patients with hypertriglyceridaemia and various components of the metabolic syndrome, fenofibrate (160 mg/day) lowered fasting and postprandial concentrations of soluble ICAM1 levels. Fenofibrate exhibits anti-migratory properties on endothelial cells by inhibiting VEGF-mediated Akt phosphorylation.

There is evidence also that the pro-inflammatory cytokines interleukin 1β and TNFα are raised in the serum and vitreous of patients with proliferative diabetic retinopathy compared with healthy controls. In a randomised placebo-controlled trial, 12 weeks of fenofibrate treatment reduced concentrations of the pro-inflammatory TNFα, interleukin 6, and interleukin 1β in plasma, as well as markers for endothelial dysfunction, although results from other studies are needed to confirm these findings. Fenofibrate could also have a protective role in the progression of diabetic retinopathy by inhibiting oxidative stress. Malondialdehyde is a lipid peroxide that is formed as a result of raised concentrations of reactive oxygen species. Malondialdehyde is raised in patients with type 1 diabetes with retinopathy. One study has shown that fenofibrate treatment (200 mg daily for 3 months) decreases plasma malondialdehyde concentrations in patients with type 2 diabetes. Lastly, omega-3 polyunsaturated fatty acids are thought to be protective against hypoxic retinopathy, but available evidence does not suggest that fenofibrate increases omega-3 concentrations in human beings.

The results of FIELD demonstrate a clear reduction in the need for laser treatment, and possible reduction in the need for laser treatment in the management of diabetic eye disease, and could also usefully inform strategies for other new drug development.

The ophthalmological findings related to the FIELD study have a number of strengths and limitations. The effects of therapy on laser treatment are robust and consistent within the main trial and the substudy. Limitations of the study include that laser treatment was one of a number of tertiary outcomes in the main trial, that data on the reason for laser treatment was collected retrospectively in about 10% of patients receiving laser treatment, and that there were 127 (12.5%) without follow-up data at the end of the substudy, including 67 (6-6%) without any follow-up data in the substudy. Another limitation is that only patients in the smaller substudy had retinal photographs taken, from which to validate the extent of retinopathy before laser treatment. Further, the effects of fenofibrate within the substudy were driven mainly by patients with pre-existing disease, whereas, paradoxically the relative reduction of laser treatment in the main trial seemed to be greater in those with no history of eye disease. This finding could possibly relate to undetected retinopathy at baseline in many of these patients who subsequently had laser treatment, but who were not part of the substudy. Consequently, although the effects on laser treatment are clear cut, the determination of the stage of the disease at which to intervene should be considered exploratory. Further evidence from ongoing trials such as ACCORD+ might provide confirmatory evidence in this regard.

The substantial benefits of fenofibrate on need for laser treatment for diabetic retinopathy are likely to be additive to those benefits arising from tight control of blood glucose and blood pressure in the management of type 2 diabetes mellitus, and emerge rapidly after treatment is commenced. The retinal benefits argue for consideration of using fenofibrate in the management of diabetic eye disease, and should be considered in the context of the other effects reported with fenofibrate in the FIELD study.

**Contributors and collaborators**


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University of Tempere; New Zealand: Christchurch Hospital, Hawkes Bay Hospital, Wellington Hospital. Retinal photography was done by: John Beaumont, Michael Bradley, David Erlich, Leanne Gardner, Ina Gouhina, Anthony Hall, Wendy Holland, Sirpa Ischenko, Erja Kokki, Allan Luckie, Tuija Märd, Keith Maslin, Pam McEvoy, James Muecke, Justin O’Dea, Paula Parkkinen, Ray Proust, Peter Rose, Anne Sala, Kieran Sindau, Andre Theron.

Outcomes Assessment Committee—N Anderson, G Hankey, D Hunt (chairman), S Lehto, C Mann, H Ronson; LP Li (outcomes officer, in attendance).

Safety and Data Monitoring Committee—C Hennekens, S MacMahon (chairman), S Pocock, A Tonkin, L Wilhelmsen; P Forder (unblinded statistician, in attendance).


Conflict of interest statement

Some members of the writing committee (ACK, PM, PAS, JO'D, TMED, ASK, RLO'C, and DT) have no conflict of interest to declare.

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References


Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial

Benjamin H Chi, Moses Sinkala, Felistas Mbewe, Ronald A Cantrell, Gina Kruse, Namwingsa Chintu, Grace M Aldrovandi, Elizabeth M Stringer, Chipepo Kankasa, Jeffrey T Safrit, Jeffrey S A Stringer

Summary

Background Intrapartum and neonatal single-dose nevirapine are essential components of perinatal HIV prevention in resource-constrained settings, but can induce resistance to other non-nucleoside reverse transcriptase inhibitor drugs. We aimed to investigate whether this complication would be reduced with a single peripartum intervention of tenofovir and emtricitabine.

Methods We randomly assigned 400 HIV-infected pregnant women who sought care at two public-sector primary health facilities in Lusaka, Zambia. One was excluded, 200 were assigned to receive a single oral dose of 300 mg tenofovir disoproxil fumarate with 200 mg emtricitabine under direct observation, and 199 to receive no study drug. Short-course zidovudine and intrapartum nevirapine were offered to all HIV-infected women, according to the local standard of care. Women who met national criteria for antiretroviral therapy were referred for care and not enrolled. Our primary study outcome was resistance to non-nucleoside reverse transcriptase inhibitors at 6 weeks after delivery. We used standard population sequencing to determine HIV genotypes. Analysis was per protocol. This study is registered with ClinicalTrials.gov, number NCT00204308.

Findings Of the 200 women who were randomly assigned to the intervention, 14 were lost to follow-up or withdrew from the study, two did not take study drug according to protocol, and one specimen was lost; 23 of 199 controls were lost to follow-up or withdrew from the study, and three specimens were lost. Women given the intervention were 53% less likely than controls to have a mutation that conferred resistance to non-nucleoside reverse transcriptase inhibitors at 6 weeks after delivery (20/173 [12%] vs 41/166 [25%]; risk ratio [RR] 0.47, 95% CI 0.29–0.76). We noted postpartum anaemia, the most common serious adverse event in mothers, in four women in each group. 20 of 198 (10%) infants in the intervention group and 23 of 199 (12%) controls had a serious adverse event, mostly due to septicaemia (n=22) or pneumonia (n=8); these events did not differ between groups, and none were judged to be caused by the study intervention.

Interpretation A single dose of tenofovir and emtricitabine at delivery reduced resistance to non-nucleoside reverse transcriptase inhibitors at 6 weeks after delivery by half; therefore this treatment should be considered an adjuvant to intrapartum nevirapine.

Introduction

Intrapartum and neonatal single-dose nevirapine are essential components of perinatal HIV prevention in many resource-constrained settings.2–6 However, in the weeks after ingestion, 20% to 69% of women have been shown to develop HIV resistance to the non-nucleoside reverse transcriptase inhibitor class of drugs.7–9 Emergence of resistance to this class of antiretroviral drugs has also been recorded when single-dose nevirapine was used in conjunction with other agents that are used to prevent perinatal HIV transmission, such as zidovudine10,11 and a combination of zidovudine and lamivudine.12 The long-term effect of these transient resistance mutations on later antiretroviral therapy (ART) is not completely understood, especially when ART is initiated more than 6 months after maternal exposure to nevirapine.13–15 The antiretroviral drugs tenofovir disoproxil fumarate and emtricitabine are in common use worldwide. Both drugs have long intracellular half-lives (50 h for tenofovir16 and 39 h for emtricitabine17) and are categorised as “probably safe” for use in pregnancy by the US Food and Drug Administration, on the basis of safety in animals. We aimed to investigate whether the addition of the tenofovir and emtricitabine combination to intrapartum nevirapine would reduce the emergence of resistance to non-nucleoside reverse transcriptase inhibitors in the weeks after ingestion. We reasoned that a single adjunctive dose of tenofovir and emtricitabine in labour, if proven effective, could reduce the adverse consequences of intrapartum nevirapine without compromising the regimen’s well known feasibility and cost-effectiveness.

Methods

Study participants

We recruited HIV-infected pregnant women in Lusaka, Zambia, who sought care at two public-sector primary...
health facilities. As part of routine perinatal HIV prevention services at these sites, all pregnant women were offered HIV-1 testing with a dual rapid-test algorithm. Those who were seropositive were immediately given a 200 mg take-home dose of nevirapine—for self-administration at the onset of labour—and then referred for ART eligibility screening. (Nevirapine was provided before referral because the local rate of attrition between antenatal and HIV care has been shown to be high.) Women who did not meet WHO maternal criteria for ART (ie, those in WHO stage I or II with CD4 cell count of greater than 200 cells per μL, or those in WHO stage III with CD4 cell count of greater than 300 cells per μL) were offered antenatal zidovudine (300 mg twice daily), starting at 32 weeks gestation.

When women presented in labour, clinic staff confirmed ingestion of intrapartum nevirapine and provided a replacement dose to those who reported that they had not taken the drug. All infants who were known to have been exposed to HIV received a single dose of nevirapine syrup (2 mg/kg) within 72 h of birth and were discharged with a 7-day course of zidovudine syrup (4 mg/kg twice daily). Nearly all HIV-infected women in our setting opted to exclusively breastfeed their exposed child for 6 months and then to wean rapidly.

We recruited women who had tested seropositive for HIV, and who were between 28 and 38 weeks of completed gestation. As part of routine care, all candidates were offered short-course zidovudine (from 32 weeks onward) and intrapartum nevirapine for perinatal HIV prophylaxis before recruitment. Women who qualified for ART to protect their own health were referred for care and were not enrolled in this study. We also excluded those who reported any previous use of antiretroviral drugs. We obtained signed informed consent from all participants at enrolment during antenatal care.

Enrolled women who had given consent and who presented to the study facility in labour were assessed by clinical staff. We randomly assigned only those who reported self-administration of single-dose nevirapine before arrival or were seen to ingest the dose after admission; were in active labour; and had no clinical indications for transfer to a tertiary-care facility.

We randomly allocated half the eligible women to receive oral tenofovir and emtricitabine (coformulated as Truvada by Gilead Sciences, Foster City, CA, USA). The dose was 300 mg of tenofovir and 200 mg of emtricitabine, given under direct observation. Women randomised to the control group did not receive any intervention above the standard of care.

We used a computer-generated block randomisation scheme, with variable block size. An independent research pharmacist prepared a set of sequentially numbered opaque envelopes before study activation. A consecutive numbered envelope was opened for each patient enrolled. After delivery, maternal venous specimens were drawn. We drew maternal plasma at 2 and 6 weeks after birth to test for drug resistance. We collected infant heel-prick specimens at birth (ie, within 8 h of delivery) and at 6 weeks of life for virological HIV diagnosis.

The study was approved by the Research Ethics Committee at the University of Zambia and the institutional review boards at the University of Alabama at Birmingham and at the Childrens Hospital Los Angeles.

Figure 1: Trial profile
At 2 weeks and 6 weeks, specimens with genotype results or with failed amplification had HIV-1 viral load of greater than 2000 copies per mL.
Procedures

We tested plasma HIV viral load with commercial tests (COBAS Ampliprep and COBAS Amplicor HIV-1 Monitor, version 1.5, standard format, Roche Molecular Systems, Branchburg, NJ, USA). We did HIV genotyping on specimens with HIV viral load of more than 2000 copies per mL in accordance with the manufacturer’s instructions. We extracted viral RNA from plasma with a commercial kit (Qiagen, Chatsworth, CA, USA). We amplified and bidirectionally sequenced the pol gene, and assembled and edited sequences with a bioinformatics program (Sequencer, Gene Codes, Ann Arbor, MI, USA). Sequences were then analysed against an HIV drug-resistance database.

We judged that mutations were present if they were detected alone or in combination with wild-type sequences (mixtures). Samples that did not amplify or were of poor quality were reamplified and sequenced with a genotyping system (ViromeSeq HIV-1 Genotyping, Celera Diagnostics, Alameda CA, USA). These assays were based on standard thresholds for detection, which generally only detect a mutant viral subpopulation of greater than 20%.

We categorised mutations of the reverse transcriptase gene that conferred drug resistance based on the recommendations of the International AIDS Society-USA Drug Resistance Mutations Group. Resistance to non-nucleoside reverse transcriptase inhibitors was assumed if we identified the mutations L100I, K103N, V106A/M, V108I, Y181C/I, Y188C/L/H, G190A, P225H, or P236L. We also categorised specimens as resistant towards tenofovir (K65R, K70E), emtricitabine and lamivudine (K65R, M184V), or zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E).

We collected dried-blood spot specimens from infants on filter paper and tested them with a commercial test (Amplicor HIV-1 DNA, Version 1.5, Roche Molecular Systems, Branchburg, NJ, USA). Two consecutive DNA PCR tests were required for diagnosis of HIV. Transmission was regarded as intrapartum if results at birth and 6 weeks were both positive, and as intrapartum or early postpartum if an infant tested HIV-negative at birth, but positive at 6 weeks (with a confirmatory positive result at least 4 weeks later).

Because high rates of non-adherence to nevirapine treatment had been previously reported in our setting, we tested for drug concentrations in cord plasma as a marker for nevirapine ingestion. Plasma concentrations were quantified by tandem mass spectrometry using a linear mass spectrometer (API 4000, Applied Biosystems, Foster City, CA, USA); we used high-performance liquid chromatography (Agilent 1200, Agilent Technologies, Foster City, CA, USA). Two consecutive DNA PCR tests were required for diagnosis of HIV. Transmission was regarded as intrapartum if results at birth and 6 weeks were both positive, and as intrapartum or early postpartum if an infant tested HIV-negative at birth, but positive at 6 weeks (with a confirmatory positive result at least 4 weeks later).

The primary outcome was maternal resistance to non-nucleoside reverse transcriptase inhibitor drugs at 6 weeks postpartum. Secondary outcomes were maternal non-nucleoside reverse transcriptase inhibitor drug resistance at 2 weeks postpartum, other maternal drug resistance (specifically to tenofovir, emtricitabine, or zidovudine) at 2 and 6 weeks postpartum, perinatal HIV transmission rates, and drug safety.

We assessed maternal haematological, hepatic, and renal function at 2 weeks after delivery, and trained study staff to monitor and report adverse clinical events for both mothers and infants. An adverse event was regarded as serious if it was fatal, life-threatening, required admission to hospital, or resulted in persistent or substantial disability. Events classified as grade 3 or above (or grade 2B or above in the case of rash) according to tables of toxic effects from the US National Institutes of Health’s Division of AIDS were regarded as serious. Adverse events were reviewed by the chair of an independent project oversight committee within 2 days of the initial report. This committee also reviewed all adverse events twice a year.

### Table 1: Antenatal and delivery characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=198)</th>
<th>Control (n=199)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26 (22-29)</td>
<td>24 (22-29)</td>
</tr>
<tr>
<td>Gravidity (pregnancies)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Parity (births)</td>
<td>2 (1-2)</td>
<td>2 (1-2)</td>
</tr>
<tr>
<td>Gestational age at enrolment (weeks)</td>
<td>30 (29-33)</td>
<td>32 (29-33)</td>
</tr>
<tr>
<td>Baseline WHO Stage III</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Baseline CD4+ lymphocyte count (cells per μL)</td>
<td>464 (208)</td>
<td>490 (200)</td>
</tr>
<tr>
<td>Baseline haemoglobin (g/L)</td>
<td>111 (13)</td>
<td>111 (11)</td>
</tr>
<tr>
<td>Baseline alanine aminotransferase (U/L)</td>
<td>12.5 (7.0)</td>
<td>12.3 (6.4)</td>
</tr>
<tr>
<td>Baseline creatinine (μmol/L)</td>
<td>45.5 (14.1)</td>
<td>46.1 (13.3)</td>
</tr>
<tr>
<td>Zidovudine initiated during antenatal period*</td>
<td>165 (83%)</td>
<td>157 (79%)</td>
</tr>
<tr>
<td>Time on zidovudine (days)</td>
<td>39 (25)</td>
<td>34 (20)</td>
</tr>
<tr>
<td>Gestational age at start of zidovudine (weeks)</td>
<td>33 (32-35)</td>
<td>33 (32-35)</td>
</tr>
<tr>
<td>Medication possession ratio†</td>
<td>100% (63%-100%)</td>
<td>100% (68%-100%)</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>38 (36-40)</td>
<td>38 (37-40)</td>
</tr>
<tr>
<td>HIV viral load suppressed at time of delivery*</td>
<td>53 (28%)</td>
<td>53 (29%)</td>
</tr>
<tr>
<td>Log HIV viral load among those not suppressed at time of delivery</td>
<td>3.9 (0.8)</td>
<td>3.7 (0.6)</td>
</tr>
<tr>
<td>Length of labour (h)</td>
<td>10.8 (8.9)</td>
<td>10.9 (8.4)</td>
</tr>
<tr>
<td>Length of membrane rupture (h)</td>
<td>1.5 (3.8)</td>
<td>1.6 (4.3)</td>
</tr>
<tr>
<td>Time from NVP ingestion to delivery, mean hours (sd)</td>
<td>7.6 (9.3)</td>
<td>7.6 (8.6)</td>
</tr>
<tr>
<td>Confirmation of ingestion of nevirapine (by detectable drug in umbilical cord plasma)*</td>
<td>159 (82%)</td>
<td>156 (81%)</td>
</tr>
<tr>
<td>Infant weight (g)</td>
<td>3173 (442)</td>
<td>3140 (413)</td>
</tr>
<tr>
<td>Apgar score at 1 min†</td>
<td>8 (8-8)</td>
<td>8 (8-8)</td>
</tr>
<tr>
<td>Apgar score at 5 min†</td>
<td>9 (9-9)</td>
<td>9 (9-9)</td>
</tr>
<tr>
<td>Reported infant breastfeeding at 6 weeks of life*</td>
<td>166 (92%)</td>
<td>161 (92%)</td>
</tr>
</tbody>
</table>

Data are number (%), median (IQR), or mean (SD), unless otherwise specified.* Based on mother-infant pairs with available data. †Medication possession ratio describes the proportion of days on which the participant had an adequate stock of zidovudine from initiation until delivery. It is used here as a proxy for adherence. †The Apgar score is a measure of the health of a newborn baby.
Statistical analysis
We calculated our target sample size of 400 women to provide 80% power to detect a large postulated effect size that we believed would be clinically relevant: a three-fold reduction in non-nucleoside reverse transcriptase inhibitor resistance—from 15% to 5%—at 6 weeks postpartum, with Fisher’s exact test (two-sided \( \alpha = 0.05 \)). We accounted for follow-up and sub-optimal adherence to nevirapine treatment. We did analyses for the per-protocol group.

Maternal non-nucleoside reverse transcriptase inhibitor resistance was assessed by sequencing the reverse transcriptase gene from maternal plasma specimens obtained at 6 weeks (primary outcome) and 2 weeks (secondary outcome) after childbirth. Specimens that were not genotyped because HIV viral load was less than 2000 copies per mL were classified as non-resistant in the primary analysis. In a complementary analysis, we assessed only specimens with viral load of more than 2000 copies per mL. We compared intraterine mother-to-child HIV transmission rates with those during and after childbirth and with overall rates according to study group.

We analysed categorical variables with Fisher’s exact test. Two-tailed \( t \)-tests were used for normally distributed continuous variables, and Wilcoxon rank-sum tests to compare medians of variables that were not normally distributed. Viral load measurements were \( \log_{10} \) transformed. We used SAS for analyses (version 9.1, SAS Institute, Cary, NC, USA). This study is registered with ClinicalTrials.gov, number NCT00204308.

Role of the funding source
The Elizabeth Glaser Pediatric AIDS Foundation played no role in study design, data collection, or data analysis, but had input into data interpretation and writing of the paper through a participating co-author (JTS). The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results
We enrolled 627 women. 227 were not eligible, either because their babies were delivered before arrival at the centre or at different facilities; they were referred for delivery ward staff, and a third because a randomisation envelope was incorrectly opened and not replaced. Table 1 shows antenatal, medical, and delivery characteristics. Overall, 322 of 397 women (81%) initiated short-course zidovudine in the antenatal period. Cord-plasma specimens were available for nevirapine drug analysis from 386 of 397 (97%) women who had been randomly assigned. From detectable drug concentrations in these specimens, we confirmed that 315 (82%) had ingested intrapartum nevirapine. This proportion did not differ between randomised groups. Of the 198 women in the intervention arm who received tenofovir and emtricitabine according to protocol, the mean time from witnessed ingestion until delivery was 3.5 (SD 4.5) h.

In patients who were given intrapartum single-dose tenofovir and emtricitabine, the maternal plasma viral load was lower after delivery than in controls. At 2 weeks postpartum, 116 of 183 women (63%) in the intervention group had undetectable viral load (ie, fewer than 400 copies per mL), compared with 93 of 177 (53%) controls (\( p=0.043 \)). Of those with detectable virus at 2 weeks, the mean log viral load was also lower (3.49 vs 3.83; \( p=0.004 \)). By 6 weeks after delivery, this difference between the intervention and control groups had disappeared, both by the proportion in which viral load was suppressed (10/183 [5%] vs 18/173 [10%]; \( p=0.114 \)) and by mean concentration in those with detectable viral load (4.40 vs 4.37; \( p=0.733 \)).

Women who had been randomly assigned to receive intrapartum tenofovir and emtricitabine were much less likely to develop resistance to non-nucleoside reverse transcriptase inhibitor drugs at 2 weeks after childbirth (RR 0.27; 95% CI 0.11–0.66), at 6 weeks (0.47; 0.29–0.76), and after childbirth (0.46; 0.28–0.74).
Articles

and cumulatively (0·44; 0·28–0·69). We noted similar results when we limited the analysis to specimens with greater than 2000 viral copies per mL, although the protective effect of tenofovir and emtricitabine was attenuated somewhat at the 2-week secondary outcome (table 2). In a secondary analysis, in which we stratified the study population according to maternal viral load at delivery (the time of nevirapine exposure), the protective effect of tenofovir and emtricitabine was most pronounced in women whose delivery viral load was greater than 10 000 copies per mL (table 3).

Of the 347 women for whom we had a specimen at 2 weeks, 24 (7%) had one mutation that conferred resistance to a non-nucleoside reverse transcriptase inhibitor, and 3 (1%) had two such mutations. Of the 339 women with an available specimen at 6 weeks, 53 (16%) women had one non-nucleoside reverse transcriptase inhibitor mutation, six (2%) women had two such mutations, and two (1%) had three mutations. Figure 2 shows the distribution of resistance mutations at 2 and 6 weeks. We did not detect any mutations associated with resistance to tenofovir, emtricitabine, or zidovudine.

Of 397 infants born to mothers in the intervention and control groups, 355 (89%) remained in the study at 6 weeks of life. Three fetuses (1%) died before delivery, nine infants (2%) died in the first 6 weeks of life, and 30 (8%) were lost to follow-up. The overall rate of perinatal HIV transmission was similar in the intervention group (10/180 [5·6%]) and the control group (14/175 [8·0%; p=0·403). This finding was consistent for intrauterine transmission (8/180 [4·4%] vs 10/175 [5·7%; p=0·635) and intrapartum/early postpartum transmission (2/127 [1·6%] vs 4/165 [2·4%; p=0·440) (table 4).

At 2 weeks after delivery, we recorded no differences in mean serum creatinine (53·77 vs 53·83; p=0·968), alanine aminotransferase (18·3 vs 20·4 U/L; p=0·643), or haemoglobin (122 vs 118 g/L; p=0·106). Seven of 198 women (4%) in the intervention group had serious adverse events, compared with nine of 199 (5%) controls (p=0·800). Four women in each group had postpartum anaemia, which was the most common serious maternal event. 20 of 198 (10%) infants in the intervention group and 23 of 199 (12%) controls had a serious adverse event. Common causes of infant morbidity were septicaemia (n=22) and pneumonia (n=8), again with no difference between groups. None of the adverse events were judged to be caused by the study intervention.

Discussion

Addition of a single dose of combined tenofovir and emtricitabine to the antiretroviral prophylaxis regimen of short-course zidovudine and intrapartum nevirapine effectively reduced the frequency of postpartum resistance to non-nucleoside reverse transcriptase inhibitors. The intervention was associated with a 73% reduction at 2 weeks and a 53% reduction at 6 weeks after nevirapine ingestion. In our setting, where most women elected to use short-course zidovudine along with intrapartum nevirapine, tenofovir and emtricitabine did not reduce perinatal HIV transmission, compared with controls (5·6% vs 8·0%; p=0·403).

Used alone or in combination, nevirapine has been an essential component of perinatal HIV prevention programmes in settings with high HIV burdens and

![Figure 2: Frequency of HIV drug resistance mutations related to non-nucleoside reverse transcriptase inhibitors at 2 weeks (A) and 6 weeks (B) after delivery](image-url)

**Figure 2:** Frequency of HIV drug resistance mutations related to non-nucleoside reverse transcriptase inhibitors at 2 weeks (A) and 6 weeks (B) after delivery

NNRTI=Non-nucleoside reverse transcriptase inhibitor. No mutations were detected at codons 41, 65, 70, 100, 184, 190, 210, 214, or 219. Percentages are based on the number of women in each group for whom specimens were available. Specimens that could not be amplified for genotyping were excluded. Results are cumulative and do not account for women with more than one mutation.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine</td>
<td>8/180 (4%)</td>
<td>10/175 (6%)</td>
<td>0·635</td>
</tr>
<tr>
<td>Intrapartum or early postpartum</td>
<td>2/172 (1%)</td>
<td>4/165 (2%)</td>
<td>0·440</td>
</tr>
<tr>
<td>Overall</td>
<td>10/180 (6%)</td>
<td>14/175 (8%)</td>
<td>0·403</td>
</tr>
</tbody>
</table>

*All p values are calculated using Fisher’s exact test.

**Table 4:** Perinatal HIV transmission at 6 weeks of life
severe resource constraints. Since 2001, for example, more than 50 000 doses of the drug have been given to HIV-infected pregnant mothers in the Lusaka, Zambia public-health sector, and this figure is representative of nevirapine use in other large programmes in the region.13 However, evidence is mounting that use of nevirapine might compromise the treatment response in some women when they later start ART with non-nucleoside reverse transcriptase inhibitors. This risk seems to be related to the length of time between nevirapine exposure and initiation of ART. Studies in sub-Saharan Africa suggest that recent exposure to single-dose nevirapine (ie, less than 6 months) might be associated with risk for virological and clinical treatment failure.13,14 If more than 6 months elapse between nevirapine use and ART initiation, the risk of compromised virological outcomes seems to fall to baseline.13,14 Nevertheless, nevirapine-induced mutations that cause resistance to non-nucleoside reverse transcriptase inhibitors are a concern in resource-constrained settings, where drugs such as nevirapine and efavirenz are common components of first-line antiretroviral regimens,15 and options for second-line treatment are limited.

Use of short-course adjunctive antiretroviral drugs to reduce resistance to non-nucleoside reverse transcriptase inhibitor after intrapartum use of nevirapine has been investigated by others. In a randomised trial in South Africa, the frequency of mutations that cause resistance to non-nucleoside reverse transcriptase inhibitors after intrapartum use of nevirapine was reduced from 57% in controls to 13% in women who received a 4-day course of zidovudine and lamivudine, and to 9% in those who received a 7-day course of zidovudine and lamivudine.19 Similar reductions have been seen in the setting of short-course antenatal zidovudine and lamivudine and intrapartum nevirapine. When zidovudine and lamivudine was started from 32 weeks gestation onward and continued for 3 days after nevirapine ingestion, the frequency of non-nucleoside reverse transcriptase inhibitor mutations declined from 33% (in historical controls) to 1%.20 Unfortunately, use of zidovudine and lamivudine in this way induced viral resistance to lamivudine, which was then associated with treatment failure in women who started ART with lamivudine.21

The primary advantage of our study intervention is its simplicity. We reasoned that a single-dose approach would lead to greater adherence and acceptability than longer regimens;22 and would thus be appropriate for settings where intrapartum nevirapine is prescribed. Despite its proven efficacy, however, the regimen might need further optimisation. Addition of a second dose of tenofovir and emtricitabine—either at discharge from the labour ward or in the days after delivery—might further reduce mutations that confer resistance to non-nucleoside reverse transcriptase inhibitors and also preserve the simplicity of the regimen. We classified specimens with viral load of less than 2000 copies per mL as non-resistant in our primary analysis. Because resistance to non-nucleoside reverse transcriptase inhibitors develops despite high viral replication, and because plasma viral load was much lower with the tenofovir and emtricitabine intervention than in controls, exclusion of specimens under this viraemia threshold would result in an incorrectly low assessment of the efficacy of the intervention. On the other hand, some of the specimens with fewer than 2000 copies of virus per mL could potentially contain HIV that is resistant to non-nucleoside reverse transcriptase inhibitors, but could be incorrectly categorised because the overall plasma viral burden is too low to allow sufficient amplification for genotyping. By this argument, these same specimens would become detectable by population genotyping at a later point, once concentrations of antiretroviral drugs had waned and plasma viral concentrations increased. To include specimens with viral load of fewer than 2000 copies per mL, and to classify them as non-resistant would thus underestimate the emergence of resistance to non-nucleoside reverse transcriptase inhibitors. Because of this dilemma, and to facilitate direct comparison of our results with those of other studies, we have presented the data both ways (ie, with and without specimens with fewer than 2000 viral copies per mL). However, our main finding—a reduction in non-nucleoside reverse transcriptase inhibitor resistance at 6 weeks—did not differ with these methods of analysis.

We did not detect HIV mutations associated with tenofovir and emtricitabine resistance in the intervention group. This result is especially relevant now that both drugs have been incorporated into first-line treatment in many African countries, including Zambia.23 The frequency of K103N mutations in our study increased from 2 weeks to 6 weeks postpartum, as has been described in other regional studies.24,25 However, the proportion with Y181C/I mutations remained stable. None of the women allocated to the intervention group developed a mutation at codon 181. We cannot explain this result.

Our results for rates of mother-to-child HIV transmission with short-course zidovudine and intrapartum nevirapine were higher than the 2% reported in clinical trials,26 but similar to the rates reported in cohorts in Côte d’Ivoire and Botswana.27-29 This finding could be attributed to the nearly universal practice of breastfeeding in African settings, or to regional differences in HIV subtypes. In our study, most transmission (18 of 24 cases) occurred during the intrapartum period, because women in our study started antenatal zidovudine at late gestation, on average. Although the intervention was not associated with significant differences in perinatal HIV transmission, our study was not sufficiently powered to assess this outcome. Future clinical trials should investigate perinatal HIV transmission as a primary outcome.
We recognise several limitations of our study. First, the HIV genotyping assays that we used could only detect viral mutations that are found in at least 20% of the overall HIV population. We therefore need to investigate the efficacy of single-dose tenofovir with emtricitabine in HIV minority populations. Second, our eligibility criteria for maternal HIV status might have introduced selection biases, since we excluded individuals at greatest risk for developing resistance—those with advanced HIV disease (and thus higher concentrations of circulating virus). Third, high uptake of antenatal zidovudine contributed to the third overall viral burden in study participants, which could have reduced the frequency of resistance to non-nucleoside reverse transcriptase inhibitors. Because reductions in resistance were greatest in women with the highest viral burden, the effect of the intervention on drug resistance might in fact be higher in settings where ART (or short-course zidovudine) is poorly accessible. Fourth, because resistance data for intrapartum nevirapine—can substantially reduce resistance in women with HIV-1 subtype C, compared with other subtypes A and D, after the administration of single-dose NVP. In J Infect Dis 2005; 192: 39–47.

We showed that a single dose of tenofovir and emtricitabine—taken with antepartum zidovudine and intrapartum nevirapine—can substantially reduce non-nucleoside reverse transcriptase inhibitor resistance mutations at 2 weeks and 6 weeks after ingestion. Despite its effectiveness, this intervention might need modification to achieve the optimum protective effect. Nevertheless, it is an important adjunct to regimens that incorporate intrapartum nevirapine and should be considered in settings where drug combinations to be taken over several days might be impractical for patients or for the local health infrastructure.

Contributors
BC and JSAS developed the study protocol, provided study oversight, designed the analysis plan, interpreted the data, and wrote the paper. MS, CK, NC, and ES contributed to the study concept, interpreted the data, and provided critical revision of the manuscript. RC and GK provided data analysis. CK, NC, and ES contributed to the study concept, interpreted the data, and edited the draft. FM provided critical revision of the manuscript. RC and GK provided data analysis.

Conflict of interest statement
We declare that we have no conflict of interest.

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Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials

Robin Christensen, Pernelle Kruse Kristensen, Else Marie Bartels, Henning Bliddal, Arne Astrup

Summary

Background Since the prevalence of obesity continues to increase, there is a demand for effective and safe anti-obesity agents that can produce and maintain weight loss and improve comorbidity. We did a meta-analysis of all published randomised controlled trials to assess the efficacy and safety of the newly approved anti-obesity agent rimonabant.

Methods We searched The Cochrane database and Controlled Trials Register, Medline via Pubmed, Embase via WebSpirs, Web of Science, Scopus, and reference lists up to July, 2007. We collected data from four double-blind, randomised controlled trials (including 4105 participants) that compared 20 mg per day rimonabant with placebo.

Findings Patients given rimonabant had a 4.7 kg (95% CI 4.1–5.3 kg; p<0.0001) greater weight reduction after 1 year than did those given placebo. Rimonabant caused significantly more adverse events than did placebo (OR=1.4; p=0.0007; number needed to harm=25 individuals [95% CI 17–58]), and 1.4 times more serious adverse events (OR=1.4; p=0.03; number needed to harm=59 [27–830]). Patients given rimonabant were 2.5 times more likely to discontinue the treatment because of depressive mood disorders than were those given placebo (OR=2.5; p=0.01; number needed to harm=49 [19–316]). Furthermore, anxiety caused more patients to discontinue treatment in rimonabant groups than in placebo groups (OR=3.0; p=0.03; number needed to harm=166 [47–3716]).

Interpretation Our findings suggest that 20 mg per day rimonabant increases the risk of psychiatric adverse events—ie, depressed mood disorders and anxiety—despite depressed mood being an exclusion criterion in these trials. Taken together with the recent US Food and Drug Administration finding of increased risk of suicide during treatment with rimonabant, we recommend increased alertness by physicians to these potentially severe psychiatric adverse reactions.

Introduction

The prevalence of obesity continues to increase worldwide, and there is a demand for effective and safe anti-obesity agents that can produce and maintain weight loss and improve comorbidities. Obesity is producing several health-related consequences. Weight loss of 5–10% of bodyweight, irrespective of how it is achieved, is associated with improvements in cardiovascular risk profiles and reduced incidence of type 2 diabetes. Non-pharmacological treatment can be effective, but success rate in the long term is low. Obesity guidelines recommend that anti-obesity pharmacotherapy is to be regarded as a potentially important adjunctive treatment to non-pharmacological therapy for patients with a body-mass index (BMI) greater than or equal to 30 kg/m², or a BMI of 27.0–29.9 kg/m² with one or more major obesity-related comorbidities. The anti-obesity agent rimonabant (acompia, Sanofi-Aventis, Paris, France), has been approved by the European Agency for the Evaluation of Medicinal Products (EMEA) in June, 2006, and is available in Argentina, Austria, Denmark, Finland, Germany, Ireland, Norway, Sweden, Greece, and the UK.

Rimonabant is a selective antagonist of the cannabinoid type 1 receptor, and it is the first member of a new class of compounds that targets the endocannabinoid system, which has been shown to be involved in the central and peripheral regulation of food intake and the CNS rewarding system. So far, four clinical trials on rimonabant have been published, and all show an increased weight loss compared with placebo of 4.6 kg over 6–12 months, with few tolerability or safety concerns. In the Rimonabant in Obesity (RIO)-Europe study, the investigators concluded that rimonabant was generally well tolerated with mild and transient side-effects. However, the individual trials showed trends to increases in depressed mood, depression, and severe adverse events. Furthermore, because patients with serious mental illness were excluded from the RIO programme, the estimates of the potential psychiatric side-effects of the drug are conservative. Rimonabant was recently assessed by the US Food and Drug Administration (FDA), and coinciding with the submission of this paper, the FDA’s Advisory Committee unanimously concluded that more detailed safety information about rimonabant in larger patient numbers over the long term was needed before the drug could be approved.

We aimed to do a meta-analysis of rimonabant studies to assess efficacy and safety of the drug, emphasising psychiatric adverse events such as depressive disorders that could potentially lead to suicide.

Methods

Search strategy and selection criteria

Five bibliographic databases (Medline from mid-1950s, Embase from 1980, Web of Science from 1945–54, Scopus from 1966, and the Cochrane Library) were searched up...
to November, 2006, for randomised controlled trials investigating rimonabant and weight loss. Search terms were (“rimonabant” OR “Acomplia” OR [“antagonist” AND “cannabinoid” AND “receptor”]) AND (“obesity” OR “weight loss” OR “overweight” OR “weight reduction” OR “slimming”) AND “controlled”. All clinical trials relating rimonabant to weight loss were identified. The reference lists of review articles and of included studies were searched to identify other potentially eligible studies. There was no limitation on language.

Only double-blind, randomised controlled trials using rimonabant for weight loss in overweight or obese participants were eligible for inclusion. Included studies had to first, enrol patients with BMI levels of 30 kg/m² or greater or 27 kg/m² or greater plus one or more obesity-related comorbidity, and second, include a placebo control group. Studies assessing any of the following terms were included: “rimonabant”, “acomplia”, “(endo) cannabinoid antagonist”, “SR141716”, and “SR141716A” (phase I and II codes for rimonabant).

Data extraction and quality assessment
Two investigators (PKK, EMB) did the literature search and reviewed the results. Full articles were retrieved for further assessment if the information in the abstract suggested that the study: (1) compared rimonabant with placebo or any other intervention; (2) included participants who where overweight or obese; and (3) assessed weight loss (in kg) as outcome. Two investigators (RC, PKK) were responsible for the assessment and extraction of data. The efficacy outcomes were the difference in mean weight change and the number of individuals achieving at least 10% weight reduction handled as a dichotomous responder criterion. The Jadad assessment method (Instrument to Measure the Likelihood of Bias)4 for quality assessment of randomised controlled trials was used as a guide to assess study quality. Quality of the included studies was assessed independently by two reviewers (RC, PKK) and any differences were resolved at the subsequent consensus meeting (AA).

Statistical analysis
We calculated the weighted mean difference for the difference in mean weight change, standardised mean difference for the hospital anxiety and depression scale (HADS) score, and odds ratios (OR) for dichotomous outcomes. Since asymptotic results can be unreliable when the distribution of the dichotomous data is sparse (as would be expected for serious adverse events, depression, and anxiety), we used exact methods for the calculation of the confidence intervals around the ORs. However, since the confidence coefficient for these exact confidence limits is not necessarily exact on a nominal level, these confidence limits are conservative, which is the recommended approach when handling sparse data.19 We applied the Fisher’s exact test to calculate the exact probabilities of the possible (2×2) tables, enabling us to estimate the Wald test associated variance, corresponding to the ratio of its estimate (log-OR) to its standard error. Accordingly, these variances are applicable for subsequent mixed-effects meta-analysis. All analyses were based on data reported as intention to treat, for which all RIO studies applied the last observation carried forward (LOCF) techniques for missing outcome data.

To combine the individual study results we did meta-analyses using SAS software (version 9.1.3), applying a restricted maximum likelihood (REML) method to estimate the between study variance and the combined efficacy and safety data.20,21 We examined heterogeneity between trials with a standard Q-test statistic (testing the hypothesis of homogeneity),21 and present the P value, which can be interpreted as the percentage of total variation across several studies due to heterogeneity.22 On the basis of combined OR values, we estimated the number needed to treat and the number needed to harm, with 95% CIs, since this method enables direct translation into clinical practice; these data were calculated on the basis of the combined OR measure, applying the overall event rate in the placebo group as a proxy for baseline risk.21 To investigate potential sources of clinical heterogeneity, we assessed the extent to which study-level variables were associated with safety by fitting REML-based metaregression models.24
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

**Results**

We identified 227 studies in the database searches (figure 1). If a study contained phases for both weight loss and weight maintenance, we included only data from the weight loss phase. After review of the identified studies, 57 were identified and retrieved for further scrutiny. We included only four randomised placebo-controlled, double-blind trials,\textsuperscript{10–13} which were of high quality (Jadad assessment score of about 5) and met the inclusion criteria. All included trials were in the RIO programme (RIO-Europe,\textsuperscript{10} RIO-Lipids,\textsuperscript{11} RIO-North America,\textsuperscript{12} and RIO-Diabetes\textsuperscript{13}), which investigated the efficacy and safety of rimonabant for treatment of obesity, diabetes, and metabolic disorders related to obesity.

Table 1 shows the average baseline characteristics of the included studies. The trials were undertaken between 2001 and 2005 (published in 2005–06), and varied in participant size (table 1). All trials were multicentre studies and 4105 participants were assessed in total (focusing solely on the intention-to-treat individuals receiving either 20 mg per day or placebo). The length of the trials varied from 12 months to 24 months. However, all the studies published detailed statistics after 1 year of treatment. The manufacturer Sanofi-Aventis sponsored all the included studies. The studies had the same primary endpoint and similar secondary endpoints (adapted to the specific population recruited in the study and the tests undertaken). The scheduled visits were planned at the same time-points. After a weight maintenance diet for 4 weeks, patients who were compliant to dietary instruction and coping with therapy were randomly assigned to placebo, rimonabant 5 mg per day, or rimonabant 20 mg per day, in addition to a hypocaloric diet (600 kcal per day deficits).

The objectives of all the available studies were to establish the long-term (1 year) efficacy and safety of rimonabant in the treatment of obesity and metabolic disorders related to obesity.
Since all analyses were based on published intention-to-treat (LOCF) data, we extracted the exact number of patients randomly assigned and who completed the first year of treatment from the studies’ trial profiles (CONSORT recommended). The OR values associated with the individual study’s 2×2 cross-table of reported adherent individuals (who completed 1 year of treatment) were consistent when rimonabant was compared with placebo (P=0.06). There was no reason to suggest a rejection of the hypothesis of homogeneity based on the Cochran Q test (Q=0.65; p=0.89), with the likelihood of completing the 1 year therapy with rimonabant or placebo being equal (OR=1.12; 95% CI 0.99–1.28). These data correspond to 1486 (59%) of the individuals randomly assigned to rimonabant for 1 year, and 932 (58%) taking placebo.

Compared with placebo, rimonabant therapy resulted in a greater reduction in bodyweight of 4.7 kg (95% CI 4.1–5.3) than did placebo (p=0.0001). All studies reported greater reductions in bodyweight in the rimonabant group than in the placebo group (figure 2). Some heterogeneity between the individual efficacy estimates was evident when we compared the magnitude of weight reduction (Q=8.02; p=0.05), corresponding to a high effect on the combined estimate (I²=62.6%). Individuals receiving rimonabant therapy were five times more likely to achieve at least 10% weight loss (OR=5.1 [95% CI 4.1–6.7]; p=0.0001) than were those taking placebo (figure 2). On the basis of the average number of responders within the rimonabant and placebo groups (639 [26%] and 106 [7%], respectively), this OR corresponded to a number needed to treat of six individuals (95% CI four to eight).

Mood was assessed with HADS at baseline and every 3 months. HADS contains seven items to assess depressive symptoms and seven items to assess anxiety symptoms, with scores ranging from 0 to 3 for each item. Depressive and anxiety symptoms are separately summarised. Scores of 0–7 are regarded as normal, 8–10 represent borderline symptoms, and 11 is regarded as high enough to warrant further assessment of the patient. Questions about suicidal thoughts are not part of the questionnaire.

All four individual studies reported HADS subscores for depression and anxiety. Since the RIO-Europe study did not report changes from baseline, we estimated the group mean differences as the standardised mean difference. There was no significant difference between rimonabant and placebo in regard to the depression subscore, whereas the increase in the anxiety score was greater in the rimonabant group than in the placebo group (table 2).

Adverse events were more likely to arise with rimonabant treatment than with placebo (figure 3). The Cochran Q test for homogeneity suggested that the effect of rimonabant on adverse events was much the same in all the studies (I²=0%; Q=0.58; p=0.90). Patients

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<th>Rimonabant</th>
<th>Placebo</th>
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<th>Depression (p=0.21)</th>
<th>Anxiety (p=0.0009)</th>
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<tr>
<td>Rimonabant</td>
<td>Placebo</td>
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**Table 2:** Hospital anxiety and depression (HAD) scale subscores for all eligible studies

![Figure 3](https://www.thelancet.com)
Depressed mood disorders consisted of depression, major depression, depressive mood, and depressive symptoms. To analyse this endpoint we used the composite endpoint depressed mood disorder also for RIO-Lipids (estimated as the sum of subcategories). More psychiatric disorders were evident in the rimonabant groups than in the placebo groups leading to discontinuation (figure 4). Patients assigned to rimonabant were 2.5 times more likely to discontinue in the trial because of depressive mood disorders than were those receiving placebo (74 [3-0%] vs 22 [1-4%]; OR=2.5 [1-2–5-1]; p=0-01; number needed to harm=49 individuals [19–316]; figure 4). Furthermore, anxiety caused more frequent discontinuation in rimonabant groups than in placebo groups (26 [1-0%] vs 5 [0-3%]; OR=3.0 [1-1–8-4]; p=0-03; number needed to harm=166 individuals [47–3716]; figure 4).

To explore the reasons for heterogeneity we undertook multiple metaregression models to reduce the between-study variance, based on the study-level covariates shown in table 1. We only focused on covariates that were able to reduce the effect of heterogeneity for two of the outcome measures: the log-OR values considering the number of patients with depressed mood and serious adverse events. We noted an association between the OR of depressed mood and the average triglyceride concentration at baseline, which could suggest that high concentrations of triglyceride at baseline might be a predictor for individuals who are likely to have depression during their use of rimonabant. Mean age at baseline seemed to be a predictor of the log OR for serious adverse events, suggesting that elderly people are more likely to have serious adverse events during treatment with rimonabant than are younger patients.

**Discussion**

Four trials in the RIO programme assessed the efficacy and safety of the anti-obesity agent rimonabant compared with placebo, and our meta-analysis has shown that rimonabant therapy produced a greater weight loss than did placebo. Patients who were allocated to rimonabant were much more likely to achieve a 10% weight reduction after 1 year compared with those allocated to placebo. These figures are in agreement with the outcome of a Cochrane meta-analysis, and suggest that rimonabant is similar to or slightly better than existing weight-loss drugs.

A meta-analysis of 11 orlistat trials and five sibutramine trials lasting 1 year or longer showed that patients given orlistat lost 2.7 kg (95% CI 2.3–3.1) more weight, and patients taking sibutramine lost 4.3 kg (3.6–4.9) more weight than did those taking placebo. The intensity and the enforcement of the restriction in calories in the RIO programme was fairly weak, and produced only modest weight loss of less than 2 kg in the placebo groups. However, the more strictly the
energy restriction is enforced and adhered to, the greater weight loss that is seen in both treatment groups, thus leaving little room for an appetite suppressant such as rimonabant to further reduce energy intake and produce weight loss. With a more effective dietary treatment programme, the additional weight loss produced by rimonabant would probably be less than that we reported.

In the RIO trials, no follow-ups were reported after discontinuation of active treatment, thus any weight regain could not be assessed. As with other weight-loss drugs, relapse is expected to occur after treatment has ended, and to achieve weight maintenance and maintain the improvement of the cardiovascular and diabetes risk factors the drug needs to be taken for life.

In our meta-analysis, patients with type 2 diabetes achieved a lower placebo-subtracted weight reduction with rimonabant than did non-diabetic patients, which is consistent with the general observation that weight loss is more difficult to achieve in patients with type 2 diabetes.29

Obesity has been shown to be associated with depression in the general population and in clinical samples, especially in women and severely obese men.31 Obese individuals who are seeking treatment are especially prone to depression. Depression has been reported to range up to 48% in these individuals, and this proportion increases as the severity of obesity increases.32,33 Obese women are 20% more likely to report suicidal ideation and 23% more likely to have made a suicide attempt in the past year compared with non-obese women.34 By contrast with the Cochrane review,7 we found it pertinent to assess the effect of rimonabant on psychiatric events with a focus on mood and depression. Because of the limitations of the trials, the risk of a severe psychiatric adverse event could not be examined, and the assessment could be achieved by only two different analyses: changes in the HADS score and discontinuation of treatment because of depressive mood disorder and anxiety.

We noted a greater increase in anxiety reported by the HADS score in participants taking rimonabant than in those taking placebo, but we failed to find any effect on depression. However, HADS is generally not used as a primary outcome measure in clinical trials of depression, but it is regarded as an acceptable method to screen for depression and anxiety primarily in non-psychiatric patients.35 According to the RIO protocols, an increase in the HADS score above 11 would imply that the patient should be seen by a psychiatrist for further assessment, but none of the RIO trials reported the number of participants who were discontinued from trials after psychiatric consultations. Another limitation of HADS is the absence of questions investigating suicidal thoughts.

Our meta-analysis has shown that more obese people in the 20 mg per day rimonabant groups than in placebo groups were taken off treatment because of depressed mood disorders. Participants given rimonabant were also at greater risk to discontinue treatment because of an increased risk of developing anxiety.

Our study had several limitations mainly because of the absence of access to all available sources reporting safety data, including unpublished phase 2 trials and several studies in progress, but also because of an absence of consistent reporting of psychiatric severe adverse effects. Additionally, the endpoint reported in the studies was depressed mood disorders, which consisted of depression, major depression, depressive mood, and depressive symptoms, and these disorders have substantially different severity and clinical implications.

Our analysis did not allow examination for psychiatric disorders other than depression and anxiety. However, according to the FDA analysis, rimonabant treatment led to more adverse events than did placebo: irritability, insomnia, stress, and nervousness were present in more than 1% of the treated patients. Panic attacks, agitation, nightmare, and abnormal dreams were more frequently reported by patients treated with rimonabant than with placebo.35 Although the number of patients discontinuing therapy because of adverse events seemed to be small, high study attrition rates raise the possibility that some events were not documented.

Moreover, in all the RIO studies the enrolled patient populations were highly selected, since patients with a past history of severe depression or those with present severe psychiatric illness were excluded. Antidepressant treatment was not permitted and warranted mandatory treatment discontinuation, as prespecified by the original RIO protocols. Information about depression, depressed mood, anxiety, etc, was self-reported, which means that under-reporting bias could have been present. For these reasons, our estimates of depressive mood disorders are probably conservative.

Our findings strongly accord with the FDA report about the safety of rimonabant that was released after the initial submission of the present paper, although the investigators did report endpoints other than those reported in our analysis. The FDA reported in their meta-analysis of RIO studies that 26% of people given rimonabant 20 mg versus 14% of those given placebo had a psychiatric symptom reported as an adverse event. They noted that 9% of participants given rimonabant 20 mg versus 5% given placebo reported symptoms of depression (depressed mood, depression, depressive symptom, or major depression), and consistent with our findings these incidents often led to withdrawal of the drug. The FDA further reported that the overall relative risk for psychiatric adverse events in the rimonabant 20 mg group versus placebo group was 1.9 (95% CI 1.5–2.3). The number of participants needing an anxiolytic or hypnotic agent for a psychiatric adverse event was 185 (9%) taking rimonabant 20 mg, 102 (5%) taking rimonabant 5 mg, and 66 (4%) taking placebo. Another 104 (5%) taking rimonabant 20 mg, 88 (4%) taking rimonabant 5 mg, and 46 (3%)
taking placebo needed an antidepressant agent for a psychiatric adverse event.

The OR for the incidence of suicide was examined by the FDA from all available studies, including smoking cessation trials, and was found to be 1·9 (1·3–3·1) for 20 mg rimonabant versus placebo. When limited to seven obesity studies, including the unpublished and continuing trials, the OR for incidence of suicide for 20 mg rimonabant versus placebo was 1·8 (0·8–3·8). In the entire database for rimonabant clinical trials, there have been only two deaths from suicide—one in RIO North America in a patient taking rimonabant 5 mg and one in a study in progress in a patient taking rimonabant 20 mg.15

The use of pretreatment markers to identify obese patients at high risk for developing depressed mood disorders would be of great clinical importance. We therefore looked for possible predictive baseline markers, and found that high triglyceride concentrations were associated with an increased probability of having depression during treatment with rimonabant. In published work there is suggestive evidence from cross-sectional studies that lends support to a link between high triglyceride concentrations and depression,16,17 but any causal relation remains to be established. Furthermore, increasing age seemed to be a predictor of serious adverse events arising from rimonabant, which could be because of altered pharmacokinetics. These findings deserve to be further addressed, and we suggest that the available raw data is provided from every patient in all existing trials, enabling an individual patient data meta-analysis to be undertaken.18 Such a meta-analysis is seen as a gold standard compared with the study-level meta-analysis.19

This would be the simplest way to investigate the safety concerns proposed by the present study, and by the FDA analyses, and also to address whether the psychiatric adverse events are associated with the magnitude of the weight loss.

Although all the included trials excluded patients with existing depression, or those with a history of depressed mood a priori, this selected population of obese individuals had an increased risk of developing depressive mood disorders during 20 mg per day rimonabant therapy. That obese patients who are prescribed rimonabant in clinical practice are less likely to be screened for depression disorders than the participants in the trials is a matter of concern. Consequently, the number needed to harm could be much lower than this finding in clinical practice. Patients who seek treatment in clinical practice are often obese women with less comorbidity, and for this group the risk of severe adverse events is less acceptable.

Other potential anti-obesity drugs that increase the risk of depression have been withdrawn because of cases of suicide ideation, suicide attempts, and death from suicide.20 The findings of our meta-analysis suggest that the potential of rimonabant to induce depressive symptoms and depression in overweight patients needs greater attention.

Contributors
RC participated in the study conception and design, the acquisition of data, the analysis and interpretation of data, drafting of the manuscript, revision of the manuscript, and the statistical analyses. PKK participated in the study conception and design, the acquisition of data, the analysis and interpretation of data, and drafting of the manuscript. EMB participated in the acquisition of data, critical revision of the manuscript, and has seen and approved the final version. HB participated in the study conception and design, and interpretation of data, critical revision of the manuscript, and supervision of the study. AA participated in the study conception and design, interpretation of data, writing and revisions of the manuscript, and supervision of the study. All authors have seen and approved the final version of the manuscript.

Conflict of interest statement
PKK, EMB, and HB declare that they have no conflict of interest. RC was statistical expert/consultant in the Lantus medical expert panel for Sanofi-Aventis (Denmark) in 2006. AA participates in several advisory boards for biotechnology and pharmaceutical companies, some of which are developing CB-1 antagonists for treatment of obesity. AA is president of the International Association for the Study of Obesity (IASO), which had received funding from Sanofi-Aventis when he was president-elect. AA participated in the Danish rimonabant advisory board for Sanofi-Aventis, until its closure in June, 2006.

Acknowledgments
We thank the personal and scientific support of Bente Danneskiold-Samsøe, (MD, Head of The Parker Institute) and the linguistic support of Tina Cuthbertson. This study was supported by grants from the Center for Pharmacogenomics, University of Copenhagen, The Oak Foundation, the H:S Research Foundation, and Diabesity EC-FP6 (contract number: LHLM-CT-2003-503041).

References
12 Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 2006; 295: 761–75.


Apparantly untreatable hypertension

Igor Mamkin, Rachid A Elkoustaf, Sundaram V Ramanan

A 54-year-old man had a blood pressure of 220/120 mm Hg, despite the use of hydrochlorothiazide, atenolol, amlodipine, and hydralazine. Abdominal MRA revealed bilateral renal artery stenosis, which was confirmed by renal arteriography (figure). The age and sex of the patient, and the appearance of the arteries, led us to conclude that the stenosis was caused by atherosclerosis—which accounts for 90% of cases of renal artery stenosis. It is uncertain whether stent insertion is more effective than medication alone, in treating atherosclerotic renal artery stenosis. In this case, a stent was inserted into each artery, and the blood pressure fell—but only to 150/85 mm Hg, even though the patient was taking hydrochlorothiazide, metoprolol, and amlodipine. We concluded that the patient had microvascular kidney disease, as well as renal artery stenosis.
Stillbirth

Gordon C S Smith, Ruth C Fretts

In the UK, about one in 200 infants is stillborn, and rates of stillbirth have recently slightly increased. This recent rise might reflect increasing frequency of some important maternal risk factors for stillbirth, including nulliparity, advanced age, and obesity. Most stillbirths are related to placental dysfunction, which in many women is evident from the first half of pregnancy and is associated with fetal growth restriction. There is no effective screening test that has clearly shown a reduction in stillbirth rates in the general population. However, assessments of novel screening methods have generally failed to distinguish between effective identification of high-risk women and successful intervention for such women. Future research into stillbirth will probably focus on understanding the pathophysiology of impaired placentation to establish screening tests for stillbirth, and assessment of interventions to prevent stillbirth in women who screen positive.

Introduction

Stillbirth accounts for 60% of all perinatal deaths and 75% of all potentially preventable losses (defined as perinatal death of a normally formed infant weighing 1000 g or more). Stillbirth is ten times more common than sudden infant death syndrome. Moreover, although rates of sudden infant death syndrome have greatly fallen over the past 10–15 years, there has been a recent slight rise in the rate of stillbirth in England and Wales, and the causes are unknown. The aim of this Seminar is to provide an overview of the causes of stillbirth and to summarise present practice and future strategies to reduce the number of stillbirths. We focus on stillbirths in the developed world where fetal death occurs before the onset of labour.

Definition

WHO defines stillbirth as a fetal death late in pregnancy, and individual countries define the gestational age at which a miscarriage becomes a stillbirth. The perinatal period is defined as 22 weeks or more of gestation (154 days) or, if the gestational age is unknown, it includes infants with a birthweight of 500 g or more and ends 7 days after birth. For international comparison, stillbirths are defined as infants born showing no signs of life in the perinatal period. Although this definition is useful, many developed countries register stillbirths at earlier weeks of gestation, some as early as 16 weeks. Underestimates of losses at early gestations occur in all reporting systems, but a strategy that includes pregnancy losses at earlier gestations improves the reliability of reporting stillbirth rates at later gestations. Obtaining reliable estimates of the number of stillbirths in developing countries is especially difficult since most births take place in the home and, in some remote areas, data are completely absent. Even in developed countries, there is an inconsistent approach to inclusion of therapeutic terminations for fetal anomalies that are prenatally diagnosed. Therefore, although perinatal death rates (early neonatal death and stillbirth rates combined) are useful indicators of access to, and quality of, antenatal care, these rates should be compared with caution.

Classification

Stillbirths can be subclassified according to the gestational age at birth, typically into early stillbirths (20–28 weeks’ gestation) and late stillbirths (after 28 weeks). Although this division is somewhat arbitrary, this stratification allows for fairly reliable international comparison of late losses, and allows stillbirths to be divided into those that are difficult to prevent (ie, early losses) and those that are potentially preventable (ie, late losses). Stillbirths are also subclassified by whether death occurred before or after the onset of labour—termed antepartum and intrapartum, respectively. However, the primary method for classification of stillbirth is according to the presumed cause or associated obstetric disorders. There are, however, more than 30 reported systems for classification of perinatal deaths. Early classifications included only a few subtypes—congenital malformations, immaturity, asphyxia, and others. Recent systems have attempted to obtain more information including on aberrations of fetal growth, pathological changes of the placenta, and maternal disorders. However, there is debate about whether hierarchical systems should be used and whether conditions such as growth restriction and hypertension are causes of or risk factors for stillbirth. Nevertheless, a systematic approach to classification of stillbirths is a crucial step in design of prevention strategies. Panel 1 shows a classification system based on obstetric criteria with 27 categories, focused around eight major groups.
Figure 1 shows the proportion of antepartum stillbirths in Scotland attributed to these groups, between 1992 and 2001.

Panel 1: Modified version of the Wigglesworth system for classification of perinatal deaths by obstetric causes

**Congenital anomaly**
1. CNS
2. Cardiovascular system
3. Renal
4. Alimentary (excluding diaphragmatic hernia)
5. Chromosomal
6. Biochemical
7. Other (including musculoskeletal)

**Isoimmunisation**
8. Rhesus incompatibility
9. Non-rhesus incompatibility

**Toxaemia†**
10. Severe—diastolic blood pressure of ≥110 mm Hg on two or more occasions and ≥200 mg/24 h
11. Other toxaemia

**Antepartum haemorrhage†**
12. Abruptio placentae
13. Placenta praevia
14. Other (with evidence of recurrent bleeding after the first trimester)

**Mechanical‡**
15. Breech
16. Cord prolapse
17. Other mechanical

**Maternal disorder**
18. Maternal trauma
19. Essential hypertension
20. Diabetes
21. Abdominal operations in pregnancy
22. Other (including maternal infection)

**Miscellaneous**
23. (Specify)

**Unexplained**
24. Birthweight <2500 g and <37 weeks
25. Birthweight ≥2500 g and <37 weeks
26. Birthweight <2500 g and ≥37 weeks
27. Birthweight ≥2500 g and ≥37 weeks

*Any structural or genetic defect incompatible with life or potentially treatable but causing death. †Any death with antepartum haemorrhage (APH) secondary to toxaemia, toxaemia is classified first and antepartum haemorrhage second. ‡Any death from uterine rupture, cord compression, birth trauma, or intrapartum asphyxia that is associated with disproportion, malpresentation, or breach delivery of babies weighing 1000 g or more. Deaths from anoxia or cerebral trauma should be classified as unexplained (codes 24–27) if there is no evidence of difficulty in labour. Antepartum deaths associated with cord entanglement in the absence of strong circumstantial evidence that cord compression caused death (eg, fetal death soon after external version) should be classified as unexplained (codes 24–27).

Figure 1: Causes of stillbirth with modified version of Wigglesworth classification for all singleton births in Scotland, 1992–2001

Data from 2635 antepartum stillbirths, from a total of 563,719 births (rate 4.7 per 1000). Over the same period, there were 320 intrapartum stillbirths in 561,084 singletons alive at the onset of labour. 75% of these stillbirths were anoxic, 17% were classified as caused by congenital abnormality, and the remaining 8% had diverse other causes. SGA=small for gestational age (smallest decile of birthweight for sex and week of gestation). AGA=appropriate for gestational age (rest of population). The data sources are as described in reference 13. Smith GCS, unpublished data.

In general, the study of specific causes of stillbirth has been slowed by the scarcity of uniform protocols for assessment and classification of stillbirths and falling autopsy rates. In most cases, death certificates are filled out before the results of postnatal investigations are available. The most useful information about specific causes of stillbirth comes from hospitals or regions that systematically review and classify these deaths. One such study, using data from McGill University (Canada), showed differences in the causes of stillbirth in relation to gestational age. Between 24 weeks and 27 weeks of gestation, the most common causes were infection (19%), abortion (14%), or fetal anomalies (14%). However, the contribution of infection to stillbirth rates can be technically difficult to define. There are some pathogens that are clearly causally associated with stillbirth, such as parvovirus B19, cytomegalovirus, and toxoplasma. However, there are others that might be associated with an increased risk of stillbirth, but strong evidence of a causal relation is absent (eg, colonisation with *Ureaplasma urealyticum*, *Mycoplasma hominis*, and group B streptococci).15,16

After 28 weeks of gestation, the most frequent types of stillbirth were those that were unexplained, including those associated with growth restriction, and placental abruption. A fetal death that is unexplained by fetal, placental, maternal, or obstetric factors is the most common, representing between 25% and 60% of all fetal deaths.17–20 Variation in the proportion defined as unexplained generally reflects whether the classification system allows risk factors to be included as causes—in
particular whether unexplained losses where the birthweight was small for gestational age are defined as being due to growth restriction or as being unexplained. A definitive classification system will probably continue to be elusive until the pathophysiology underlying the large number of cases without a clear direct cause is elucidated.

Stillbirth in the developing and developed worlds
A detailed discussion of stillbirth in the developing world is beyond the scope of this Seminar, and has been reviewed elsewhere.21 However, the scale and nature of the problem will be compared with that in developed countries. The greatest risk factor for stillbirth is being born in the developing world.22,23 Within developed countries, the stillbirth rate is estimated to be between 4·2 and 6·8 per 1000 births, whereas in the developing world this rate is between 20 and 32 per 1000 births (table 1).21 Where good data exist, rates of stillbirth and neonatal death in the developing world are roughly equivalent. As care improves, there is generally a greater reduction in neonatal deaths, increasing the proportion of perinatal deaths attributed to stillbirth.1 The causes of stillbirth vary in developed and developing countries (panel 2).21 An estimated 27% of stillbirths worldwide occur during labour at term or near term.22 In developed countries, fetal death during labour is rare—rates are less than one per 1000 births.23 However, in many areas of the developing world intrapartum deaths occur as frequently as one per 100 births.24 Hence, most of these deaths happen in the developing world and could be prevented with adequate obstetric care. Furthermore, common causes of antepartum losses in the developing world, such as syphilis and malaria, are also largely preventable by screening and treatment for pregnant women.11,26

These observations suggest that stillbirth prevention in the developing world could be medically fairly simple and that obstacles to prevention largely relate to factors that make delivery of basic obstetric care difficult. These include, but are not limited to, geography, financial resources available to governments, political power to effect change, availability of facilities and trained personnel, and cultural factors. This conclusion is supported by the findings of a cluster randomised controlled trial undertaken in a rural area of Pakistan (Larkana in the province of Sindh).27 Subdistricts were randomly assigned to intervention or control groups. The intervention consisted of 3 days of training for traditional birth attendants in conduct of delivery and provision of obstetric care. Outreach clinics were provided by local obstetricians because of an absence of traditional birth attendants. In the intervention subdistricts, the stillbirth rate was 50 per 1000 births, compared with 71 per 1000 in the control districts (adjusted odds ratio 0·69, 95% CI 0·57–0·83).

Maternal characteristics and risk of stillbirth
In developed countries, the most prevalent risk factors for stillbirth are nulliparity,28 advanced maternal age, and obesity (table 2). From a public-health perspective, obesity includes, but is not limited to, geography, financial resources available to governments, political power to effect change, availability of facilities and trained personnel, and cultural factors. This conclusion is supported by the findings of a cluster randomised controlled trial undertaken in a rural area of Pakistan (Larkana in the province of Sindh).27 Subdistricts were randomly assigned to intervention or control groups. The intervention consisted of 3 days of training for traditional birth attendants in conduct of delivery and provision of three antenatal visits. Outreach clinics were provided by local obstetricians because of an absence of traditional birth attendants. In the intervention subdistricts, the stillbirth rate was 50 per 1000 births, compared with 71 per 1000 in the control districts (adjusted odds ratio 0·69, 95% CI 0·57–0·83).

Table 1: Rates of stillbirth in different regions of the world

<table>
<thead>
<tr>
<th>Region</th>
<th>Stillbirth rate per 1000 deliveries (95% CI)</th>
<th>Number of stillbirths</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>23·9 (18·8–30·5)</td>
<td>3 219 428</td>
</tr>
<tr>
<td>Developed countries</td>
<td>5·3 (4·2–6·8)</td>
<td>57 865</td>
</tr>
<tr>
<td>Developing countries</td>
<td>25·5 (20·1–32·5)</td>
<td>3 161 563</td>
</tr>
<tr>
<td>North Africa</td>
<td>18·6 (14·1–24·7)</td>
<td>66 785</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>32·2 (25·4–40·9)</td>
<td>889 697</td>
</tr>
<tr>
<td>Latin America/Caribbean</td>
<td>13·2 (10·4–16·7)</td>
<td>153 162</td>
</tr>
<tr>
<td>East Asia</td>
<td>23·2 (18·3–29·5)</td>
<td>483 436</td>
</tr>
<tr>
<td>South Asia</td>
<td>31·9 (25·1–40·7)</td>
<td>1 286 231</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>12·7 (10·0–16·0)</td>
<td>144 681</td>
</tr>
<tr>
<td>West Asia</td>
<td>18·9 (14·3–24·9)</td>
<td>94 810</td>
</tr>
<tr>
<td>Eurasia</td>
<td>12·2 (9·5–15·5)</td>
<td>39 236</td>
</tr>
<tr>
<td>Oceania</td>
<td>15·8 (12·4–20·1)</td>
<td>352 448</td>
</tr>
</tbody>
</table>

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Panel 2: Commonly reported maternal risk factors for and causes of stillbirth in developing and developed countries by ranking of estimated attributable risk or importance

Developing countries
- Obstructed or prolonged labour and associated asphyxia, infection, and birth injury (low availability of caesarean-section)
- Congenitally acquired infections, especially syphilis and gram-negative infections
- Hypertensive disease, especially poor management of pre-eclampsia and eclampsia
- Poor nutritional status
- Previous stillbirth
- Congenital anomalies
- Malaria
- Sickle-cell disease

Developed countries
- Congenital or karyotypic anomalies
- Growth restriction or placental thrombosis
- Medical diseases such as diabetes, systemic lupus erythematosus, renal disease, thyroid disorders, thrombophilias, cholesterol of pregnancy
- Hypertensive disease/pre-eclampsia
- Congenitally acquired infections such as Group B streptococcus and parvovirus B19
- Smoking
- Multiple gestation

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to and quality of care are all greatly associated with risk of stillbirth. In the USA, black women are four times more likely to have no prenatal care than are white women. The combination of no prenatal care and black race puts these women at a seven-fold higher risk of stillbirth than white women who received prenatal care.33,34 Even when studies are confined to women who have received care beginning in the first trimester, black women still have a greater than three-fold risk of perinatal death compared with white women.33,34 The excess of stillbirth was attributed to higher rates of diabetes, hypertension, placental abruption, and premature rupture of membranes.33–35 An increased stillbirth rate of non-majority women compared to white women is a consistent finding even in countries that have universal access to medical care.36,37

Advanced maternal age is associated with an increased risk of stillbirth in both nulliparous and multiparous women.38 Historically, a substantial proportion of perinatal deaths seen in older women was related to lethal congenital and chromosomal anomalies.39,40 However, the introduction of population-based screening for chromosomal abnormalities and the availability of elective abortion has contributed to reduced rates of this type of perinatal death.39 Advanced maternal age is associated with an increased stillbirth rate of non-majority women compared to white women is a consistent finding even in countries that have universal access to medical care.38,39

A strategy of antepartum testing late in pregnancy has the potential to decrease late unexplained stillbirth in older women but also predicts increased induction and caesarean section rates.44

Hypertension and diabetes are two of the most common medical disorders to complicate pregnancy (affecting 7–10% and 3–5% of women, respectively).14,32,45 Population-based studies showed a two-fold to four-fold risk of stillbirth in women with diabetes.46,47 However, reports from referral centres suggest that with optimum management, including preconception care and close medical supervision, the risk of perinatal death is only marginally raised above that of the general population.42

Table 3 lists other important medical conditions associated with an increased risk of stillbirth.45

<table>
<thead>
<tr>
<th>Medical disorders associated with stillbirth risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pregnancies</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
</tr>
<tr>
<td>Chronic hypertension</td>
</tr>
<tr>
<td>Superimposed pre-eclampsia</td>
</tr>
<tr>
<td>PIH/mild pre-eclampsia</td>
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<tr>
<td>Severe pre-eclampsia</td>
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<tr>
<td>Eclampsia</td>
</tr>
<tr>
<td>HELLP syndrome</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Gestational diabetes</td>
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<tr>
<td>Type 1 diabetes</td>
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<tr>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Chronic renal disease</td>
</tr>
<tr>
<td>Mild renal insufficiency</td>
</tr>
<tr>
<td>Moderate and severe renal insufficiency</td>
</tr>
<tr>
<td>Thyroid disorders</td>
</tr>
<tr>
<td>Stable treated hyperthyroidism</td>
</tr>
<tr>
<td>Uncontrolled thyrotoxicosis</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
</tr>
<tr>
<td>Cholestasis of pregnancy</td>
</tr>
<tr>
<td>PPH=pregnancy induced hypertension. HELLP=haemolysis, elevated liver enzyme levels, and a low platelet count. Modified from reference 45 with permission from Elsevier.</td>
</tr>
<tr>
<td>Tile 2: Systematic review of epidemiological associations with stillbirth</td>
</tr>
<tr>
<td>Prevalence</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>All pregnancies</td>
</tr>
<tr>
<td>Nulliparity</td>
</tr>
<tr>
<td>Smoking &gt;10 cigarettes per day</td>
</tr>
<tr>
<td>Obesity (before pregnancy)</td>
</tr>
<tr>
<td>BMI &gt;30 kg/m²</td>
</tr>
<tr>
<td>Low educational attainment (&lt;12 years vs ≥12 years)</td>
</tr>
<tr>
<td>Previous growth-restricted infant (&lt;10%)</td>
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<tr>
<td>Previous stillbirth</td>
</tr>
<tr>
<td>Multiple gestation (reference singleton)</td>
</tr>
<tr>
<td>Twins</td>
</tr>
<tr>
<td>Triplets</td>
</tr>
<tr>
<td>Advanced maternal age (reference &lt;35 years)</td>
</tr>
<tr>
<td>&gt;40 years</td>
</tr>
<tr>
<td>Black (reference white)</td>
</tr>
<tr>
<td>BMI=body-mass index. *Odds ratio of the factor present compared with the risk factor absent. Modified from reference 14 with permission from Elsevier.</td>
</tr>
<tr>
<td>Table 3: Medical disorders associated with stillbirth risk</td>
</tr>
</tbody>
</table>
through effects on the maternal or fetal vasculature, or both.\textsuperscript{36} The associations between prothrombotic mutations and stillbirth risk are the first clear example of genetic predisposition towards stillbirth. The possibility of genetic predisposition is supported by the tendency for stillbirth recurrence, although clearly other factors could also explain this effect. The genetic epidemiology of stillbirth will probably be a major area of future research. However, the conduct of adequate studies is potentially difficult, since the rarity of the outcome means that large sample sizes are needed. Moreover, as discussed above, stillbirth is the endpoint of diverse mechanisms, and informative analyses will need to use very well defined phenotypes. In cardiovascular medicine, many studies that address obvious candidate genes for common conditions of well understood pathophysiology might be needed to establish the presence or absence of an association.\textsuperscript{11}

The fact that women with a previous stillbirth are at increased risk of stillbirth in future pregnancies is well known.\textsuperscript{37} Moreover, women with previous complicated pregnancies that resulted in a livebirth have a raised risk of future stillbirth,\textsuperscript{31} both explained and unexplained.\textsuperscript{34} A large-scale study of more than 100,000 second births in Scotland from 1992 to 1998 showed an association between delivery by caesarean section in a first pregnancy and the risk of stillbirth in the second.\textsuperscript{33} The association was with unexplained stillbirth, in particular those associated with growth restriction. The association was also evident when studies were confined to women whose previous caesarean section was done at term and after more than 10 h of labour, making previous caesarean delivery unlikely to be merely a marker for women with pre-existing medical complications. A follow-up study from Scotland has confirmed that the same association is present for births from 1999 to 2001, making the first study unlikely to be a chance finding.\textsuperscript{39} Studies from other countries, with data sources of variable quality, have been inconsistent.\textsuperscript{38–39} The strengths of the Scottish dataset are that the population is fairly racially and economically homogeneous, there is universal free access to health care, and the country obtains complete, quality assured, and detailed information on maternal characteristics, pregnancy outcome, and the cause of perinatal death. Further studies from other high quality databases will be needed to establish whether the association is consistent.

### Multiple gestations

Over the past two decades, rates of twin pregnancies have more than doubled and higher order multiples have increased by six-fold to 12-fold.\textsuperscript{60} The stillbirth rate for multiples is four-fold higher than it is for singletons (19·6 per 1000 vs 4·7 per 1000, respectively) with all types of death more common for multiples than for singletons.\textsuperscript{82} These higher rates are because of complications specific to multiple pregnancy (such as twin to twin transfusion syndrome) and increased risks of complications common to singletons and multiples, especially fetal abnormalities and growth restriction. The determinants of increased perinatal mortality in twins have been extensively reviewed elsewhere.\textsuperscript{44} Multiple gestations are a substantial contributor to overall perinatal mortality rates, and reduction in the proportion of births that are multiples represents an important area for prevention of stillbirths.\textsuperscript{19–44} The number of multiple births has risen because of an increased use of assisted reproductive technologies and a growing proportion of older mothers.\textsuperscript{44} Higher order multiples are associated with even greater rates of perinatal death,\textsuperscript{41} and many are attributable to assisted reproductive technologies. An international strategy of lowering the in-vitro fertilisation transfer rate to two embryos could substantially reduce the number of perinatal deaths associated with higher order multiple pregnancies.\textsuperscript{41}

### Trends in stillbirth

Rates of stillbirth fell greatly throughout the developed world in the second half of the 20th century.\textsuperscript{67} A longitudinal study\textsuperscript{47} of a single centre in Canada, where detailed information was available on the cause of perinatal death over 40 years, showed that the greatest reductions in stillbirth took place when strategies were developed to intervene in specific causes of fetal demise. For example, there was a 95% reduction in stillbirths because of rhesus isoimmunisation after introduction of rhesus immune prophylaxis and much the same reduction in deaths caused by intrapartum anoxia, which coincided with developments in fetal monitoring and the more liberal use of caesarean section. In northeast England, there has been a 50% reduction in perinatal deaths due to congenital abnormality between 1982–90 and 1991–2000,\textsuperscript{42} which is assumed to result from the

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**Table 4:** Acquired and inherited thrombophilia and the risk of stillbirth and comparison with other adverse outcomes of pregnancy

<table>
<thead>
<tr>
<th>Factor V Leiden homozygote</th>
<th>PT heterozygote</th>
<th>MTHFR homozygote</th>
<th>Protein C deficiency</th>
<th>Protein S deficiency</th>
<th>Anticardiolipin antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>0</td>
<td>–</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Factor V Leiden heterozygote</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>PT heterozygote</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>MTHFR homozygote</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+*</td>
</tr>
</tbody>
</table>

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\footnotesize{\textsuperscript{=Insufficient information. No studies or non-significant association, but upper limit of 95% CI >2. O=Weak or no association. Upper limit of 95% CI >2. ++=Moderate association. Point estimate of odds ratio between 2 and 5 and 95% CI excludes 1. +++=Strong association. Point estimate of odds ratio >5 and 95% CI excludes 1. IUGR=intrauterine growth restriction. PT=prothrombin G20210A. MTHFR=methylenetetrahydrofolate reductase C677T. *p=0·05, lower limit of 95% CI 0·96, point estimate 18·6.}
Stillbirth and the placenta

The pathophysiology of stillbirths caused by congenital abnormality and infection will depend on the specific condition or organism, respectively. Many of the other broad categories of cause of death, including pre-eclampsia, abruption, and unexplained stillbirth, are thought to be related to placental function. For abruption, the role of placentation is self evident and for pre-eclampsia, there is much evidence to link the disease to placentation. Similarly, there is evidence that attributes many cases of unexplained stillbirth to the placenta. About half of unexplained stillbirths have a birthweight less than the tenth percentile corrected for gestational age and parental characteristics. Hence, stillbirth associated with intrauterine growth restriction, but without any other obvious direct cause, is one of the major types of stillbirth. Poor fetal growth, without other environmental causes, is assumed to indicate poor function of the placenta. Whether poor fetal growth is simply a marker of placental dysfunction or whether it is causally associated with the mechanism of death is unclear.

Perfusion of the placenta from both the maternal and fetal side has been studied in detail, although most studies have focused on growth restriction as a proxy of stillbirth. Before pregnancy, the uterus is a high resistance circulation. During the first half of pregnancy, trophoblast invades the maternal spiral arteries, reducing resistance to blood flow in the uterine circulation. Clinically this process can be assessed by Doppler flow velocimetry of the uterine arteries. A high-resistance pattern of flow at the end of the second trimester of pregnancy is associated with an increased risk of growth restriction and stillbirth, as well as other perinatal complications. It is much more strongly associated with the risk of stillbirth at preterm gestations (figure 2). High-resistance flow on the fetal side of the placenta is also associated with an increased risk of stillbirth. Detailed study of placental ultrastructure in fetuses with high resistance patterns of umbilical artery Doppler flow velocimetry has shown that this is associated with maldevelopment of the villous tree.

The mechanisms that underlie impaired placental perfusion remain unclear. However, in some cases, the determining factors are probably related to placental dysfunction originating in very early pregnancy. In the first 10 weeks after conception, both growth of the fetus and maternal circulating concentrations of the placentally derived regulator of the insulin-like growth factor system, pregnancy associated plasma protein-A (PAPP-A), are associated with the risk of delivering an infant with low birthweight. Women with PAPP-A concentrations in the lowest 5% in the first 10 weeks after conception had a 40–50-fold risk of stillbirth attributable to growth restriction or abruption. Pathological analysis of the placenta in otherwise unexplained stillbirths related to growth restriction is consistent with chronic placental dysfunction, which is associated with focal lesions seen on macroscopic examination.

The risk of unexplained stillbirth in the absence of growth restriction was not related to concentrations of PAPP-A in early pregnancy. However, studies of placental pathological changes from such cases are also suggestive of a placental origin to this type of loss. Histopathological examination of placentae from a series of such cases showed changes suggestive of acute placental dysfunction, specifically “severely reduced vascularisation of the chorionic villi and lack of syncytiocapillary membranes” and this feature was associated with a 70-fold risk of stillbirth. The biological mechanisms underlying both acute and chronic placental dysfunction are unclear, but might include determinants of placental function such as genomic imprinting or immune interaction. Assessment of the detailed published work on placental pathological changes and stillbirth is impeded by a general absence of standard definitions and nomenclature between studies.

Clinical tests of stillbirth risk

Understanding the pathophysiology of impaired placentation and fetal growth restriction has led to the identification of tests that are associated with stillbirth.
risk. These tests include circulating concentrations of placentally derived proteins in the mother’s blood (PAPP-A, and α-fetoprotein [AFP]), Doppler flow velocimetry of the uterine and umbilical arteries, and ultrasonic assessment of the appearance of the placenta (calcification and visible lesions). None of these tests is in routine clinical use for assessment of stillbirth risk in unselected populations. However, some are done for other purposes—eg, the biochemical tests are part of population-based screening for Down’s syndrome. There is clearly the potential to use the information that a specific test result confers an increased risk of stillbirth to inform intervention. For example, it has been suggested that women with raised serum concentrations of AFP or human chorionic gonadotropin (hCG) in their second trimester should have close surveillance of their pregnancies, such as growth scans every 2–4 weeks. However, there is no direct evidence that this approach is beneficial in an unselected population. Moreover, the nature of the association with stillbirth risk is usually imprecisely known. The association between increased AFP concentration and stillbirth in nulliparous women has proved confined to preterm losses. Without this information, interventions such as routine late pregnancy growth scans or induction on achieving term gestation might be considered, but, in view of the gestational age dependence of the association, these interventions would not be expected to be effective.

Prevention of stillbirth
Prevention of intrapartum stillbirth is a cornerstone of the management of labour and delivery and has been extensively reviewed. Understanding the pathophysiology and aetiological factors for some causes of ante-partum stillbirth has led to assessment of several medical treatments, but none is in routine practice. In view of the association between thrombophilia and the risk of stillbirth, strategies could include use of low molecular weight heparin or administration of high doses of folic acid (used to return homocysteine concentrations in women with the methylenetetrahydrofolate reductase mutation, C677T, to normal). However, no high quality data exist on the effects of these interventions, and the present recommendations for pregnant women in the second half of pregnancy with a thrombophilia are that anticoagulant treatment should be for prevention of thromboembolic disease only. In view of the association between fetal hypoxia and stillbirth, some studies have assessed supplemental maternal oxygen therapy as a means of reducing perinatal death in women with a growth-restricted infant. The results from a meta-analysis of three studies with 94 women reported a 50% reduction in perinatal mortality. However, only one of the studies was blinded. This intervention is not in routine use, would be impractical in many settings, and widespread application would need confirmation of this finding in a large-scale, high-quality, randomised controlled trial. We are unaware of any other adequately investigated medical therapies shown to reduce the risk of stillbirth.

Grant and colleagues have assessed the use of kick charts to reduce ante-partum stillbirth, but they noted no difference in the stillbirth rates when the intervention and control groups were compared. Nonetheless, the stillbirth rate decreased from 4·0 per 1000 to 2·8 per 1000 in both groups, which is probably because of the Hawthorne effect. Other aspects of the published work suggest that fetal activity could be clinically important, and further research is needed to delineate the role of maternal assessment of fetal activity. Many biochemical and biophysical tests of fetal wellbeing have been assessed as a means of modifying the risk of stillbirth and these are summarised elsewhere. However, simply doing a test cannot directly affect the risk of stillbirth. Tests of fetal wellbeing can change the risk of stillbirth by informing decisions about the timing of delivery to prevent fetal death. However, delivery of the fetus incurs the risk of maternal or neonatal morbidity or mortality. Therefore, assessment of these methods includes the effect of interventions on total perinatal mortality—ie, the sum of stillbirths and neonatal deaths.

Results from a meta-analysis of randomised controlled trials shows that the use of umbilical artery Doppler flow velocimetry may reduce overall perinatal mortality in high-risk pregnancies. However, only a trend towards a reduction in perinatal mortality is reported, and the analysis is also consistent with no effect on mortality (findings from a previous meta-analysis had shown a significant reduction—significance was lost when a dubious trial was excluded). Meta-analyses of methods of fetal monitoring do not suggest any methods of fetal assessment that reduce the risk of stillbirth when used for screening in an unselected population. Some trials seem to show possible beneficial effects, such as assessment of placental maturity in the third trimester, but this has not been confirmed (or refuted) by any further trials.

Many methods of fetal assessment have been investigated in unselected populations. However, interpretation of the negative results is not straightforward, and the meta-analysis of umbilical artery Doppler in low-risk pregnancies is a good example of the difficulties of interpretation. First, the trials in this meta-analysis were designed without reliable information about how the test performed as a predictor of stillbirth in a population of low-risk women. The adequate design of an interventional trial needs knowledge of how well the test can identify women at increased risk. In the case of stillbirth, this includes both the discriminative power of the test and the gestational age dependence.

The second challenge in interpretation of these data is the failure to distinguish between the two major components of successful screening—namely, effective detection of women at increased risk and effective inter-
randomised controlled trials that directly support routine delivery. However, these interventions might be justified on the basis of epidemiological evidence of an increased risk of fetal death\textsuperscript{47,52} and by the very low risk of neonatal death associated with delivery at term.\textsuperscript{103} Indeed, even in unselected pregnancies, the lowest risk of perinatal death at term is associated with delivery at 38–39 weeks.\textsuperscript{102} However, routine induction of all women would be highly invasive and would need very large numbers of elective deliveries to prevent each loss.

The lower risk of neonatal death at term does, however, logically lead to a focus on interventions at term, since these approaches have less potential to cause harm than do those undertaken preterm. A detailed model that has assessed the probable effect of routine induction of women on the basis of a test of stillbirth risk has been described (table 5). This model shows that losses might be prevented by a structured programme of fetal assessment.\textsuperscript{44} The effectiveness of such a programme is raised with an increasing background risk of stillbirth. However, this analysis assumes a test with 70% specificity and 90% sensitivity for stillbirth (hence a positive likelihood ratio of 7). There are no data to suggest that any of the present tests of fetal wellbeing at term have this amount of predictive value. Early elective delivery is done primarily on the basis of risk factors in a woman’s previous obstetric or medical history. Perhaps the most promising approach to population-based screening is to focus on development of predictors of stillbirth at term. If an effective screening method can be developed for this event, elective delivery at 37–38 weeks would be a simple intervention that should prevent placental related losses but which would carry a low risk of neonatal death.

### Management of stillbirth

Clinical management of a stillbirth is dealt with in detail elsewhere,\textsuperscript{187} and only selected aspects will be discussed. After intrauterine fetal death, induction of labour within 24 h is usual practice. Delay of induction has theoretical risks of disseminated intravascular coagulation and infection, but these risks are small in the absence of further obvious complications, and some parents want to delay induction. Administration of mifepristone before oxytocics is widespread in the UK, although the evidence is largely by extrapolation from its use in termination of pregnancy rather than direct evidence relating to non-therapeutic losses.\textsuperscript{105,106} After delivery, the infant should be carefully inspected and findings documented in detail. Parents should be encouraged to hold their infant, although there is some evidence that this practice could be associated with increased adverse psychological and social sequelae in some women with very preterm stillbirths.\textsuperscript{107} Consent should be sought for autopsy. The procedure and the potential usefulness of the information should be explained in detail, and consent should be explicit in relation to any retention of tissue.

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**Table 5: Predicted effect of structured programme of antepartum fetal assessment at term on stillbirth rate and rates of obstetric interventions**

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio for unexplained stillbirth*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Fetal deaths per 1000 per week</td>
<td>0.4</td>
</tr>
<tr>
<td>Fetal deaths averted per week</td>
<td>1.2</td>
</tr>
<tr>
<td>Tests per pregnancy</td>
<td>3.4</td>
</tr>
<tr>
<td>Tests per fetal death averted</td>
<td>2862</td>
</tr>
<tr>
<td>Inductions per fetal death averted</td>
<td>233</td>
</tr>
<tr>
<td>Caesarean deliveries per fetal death averted</td>
<td>44</td>
</tr>
</tbody>
</table>

* Assumes base-case test characteristics (70% sensitivity, 90% specificity). Fetal deaths per 1000 pregnancies compared with no testing. Outcomes from week 37 to week 41 of gestation. Reproduced from reference 44 with permission from author and publisher.
Other postmortem investigations should be recommended, including karyotyping, gross and histopathological examination of the placenta and membranes, external examination of the infant by a pathologist when autopsy is declined, radiograph of the infant and, if available, MRI examination. The use of MRI remains to be fully ascertained, and although it is unlikely to replace full autopsy, it can provide useful information. Generally, maternal blood is obtained to test for direct causes (such as congenital infection, fetomaternal transfusion, and isoimmunisation) and risk factors (thrombophilia screen and glycosylated haemoglobin). Counselling should be offered. Finally, it is usual practice in the UK for a consultant to see the woman and her partner (if appropriate) 6 weeks after the loss to discuss their questions, to review the results of investigations, to discuss management of a future pregnancy (if planned), and to arrange further referral if needed.

Conflict of interest statement
We declare that we have no conflict of interest.

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28 Raymond EG, Cnattingius S, Kiely JL. Effects of maternal age, parity, and smoking on the risk of stillbirth. BJOG 1994; 101: 301–06.
37 Parsons L, Duley L, Alberman E. Socio-economic and ethnic factors in stillbirth and neonatal mortality in the NE Thames Regional Health Authority (NETHRA) 1983. BJOG 1990; 97: 237–44.
103 Crowley P. Interventions for preventing or improving the outcome of delivery at or beyond term. Cochrane Database Syst Rev 2000; 2: CD000270.
Most developing countries do not have fully effective civil registration systems to provide necessary information about population health. Interim approaches—both innovative strategies for collection of data, and methods of assessment or estimation of these data—to fill the resulting information gaps have been developed and refined over the past four decades. To respond to the needs for data for births, deaths, and causes of death, data collection systems such as population censuses, sample vital registration systems, demographic surveillance sites, and internationally-coordinated sample survey programmes in combination with enhanced methods of assessment and analysis have been successfully implemented to complement civil registration systems. Methods of assessment and analysis of incomplete information or indirect indicators have also been improved, as have approaches to ascertainment of cause of death by verbal autopsy, disease modelling, and other strategies. Our knowledge of demography and descriptive epidemiology of populations in developing countries has been greatly increased by the widespread use of these interim approaches; although gaps remain, particularly for adult mortality. However, these approaches should not be regarded as substitutes for complete civil registration but rather as complements, essential parts of any fully comprehensive health information system. International organisations, national governments, and academia all have responsibilities in ensuring that data continue to be collected and that methods continue to be improved.

**Introduction**

Accurate and timely data for mortality by age, sex, and cause both nationally and subnationally are essential for the design, implementation, monitoring, and assessment of health programmes and policies. In countries with well developed statistical systems, the necessary information for such descriptive epidemiology is derived from civil registration, medically certified cause of death, and population counts from regular censuses or population registers. However, the paper by Mahapatra and colleagues in this Series has convincingly shown that these data are simply not available for many countries with poorly developed statistical systems: in these countries births and deaths might not be registered completely; for those deaths that are recorded, the age at death might be misreported; the cause of death might not be certified by a physician; it might be recorded as an ill-defined cause; and could be misdiagnosed. Population numbers, needed as denominators, can suffer from errors of coverage and errors in reporting the age of individuals. These failures derive from technical and structural weaknesses, ranging from bureaucratic inefficiency and poor management of data to having inadequate incentives, or even disincentives for the population to record vital events.

Both national governments and the international community should give high priority to policies that will upgrade civil registration systems so that all countries will enjoy the benefit of a solid empirical base for health-sector planning. However, experience has shown that such improvements cannot be achieved overnight and need investment not only in administrative systems but also in public awareness. The number of countries with death registration regarded as complete (by the very rigorous standard of 90%) increased by only seven from the 1970s to the 1990s. Interim substitutes for civil registration are needed to provide national and subnational estimates of vital events and cause-specific mortality until achievement of complete civil registration with adequate certification of cause of death by a qualified medical practitioner familiar with the principles and procedures of the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). The purpose of this paper is to review the strengths and weaknesses of interim strategies for collection and analysis of data that have been developed as substitutes for complete civil registration. We also highlight how such interim measures are inadequate, and suggest targets for future development.

**Interim substitutes**

Several strategies for collection and analysis of data have been developed as interim substitutes for complete civil registration, each with its own strengths and weaknesses. Table 1 summarises the potential contributions of different strategies, and figure 1 shows where some of the strategies (eg, targeted questions in population censuses, sample registration systems, demographic surveillance sites, and household surveys) have been used around the world. These sources of data generally have to be supplemented with methods of assessment or adjustment to produce satisfactory estimates.
Unfortunately, no one strategy meets all data needs, and the strategies have to be seen as complementary rather than competitive. Existing strategies are also better at estimating some outcomes (eg, child mortality or fertility) than others (eg, adult mortality).

**The population census**

Even well developed statistical systems need to include a way to estimate denominators for mortality and fertility rates. Such denominators are expressed in terms of exposure time, (ie, the number of person-years of exposure to risk of an event such as a birth or death). Most countries with well developed systems do regular population censuses to meet this need, although some rely on population registers. However, in countries with less developed systems, the census can offer much more than merely denominators for birth and death rates through the inclusion of targeted questions. Many censuses in developing countries include summary birth histories for all women aged 15–49 (or an older age cutoff); such histories typically count the number of liveborn children for each woman and the number still alive (or equivalent the number that have died). The average number of children born alive by the age-group of the mother allows for a measure of fertility (especially if women are asked about the timing of a recent birth). The proportions of children who have died of women in different age-groups can help to estimate under-5 mortality by standard methods. Although this approach cannot estimate age patterns of child mortality, it can provide estimates of recent trends, differentials by population subgroup, and perhaps most importantly, differentials by small areas.

The working group for the 2010 round of population censuses recommended that countries without alternative sources of adult mortality estimates include questions about deaths in each household by age and sex in a reference period before the census. Methods have been developed to assess the completeness of reporting of deaths ascertained in this way; assuming that the deaths recorded are representative of the true age pattern of deaths, the coverage relative to the coverage of population denominators can be estimated by accounting identities of population dynamics. One such identity is that the death rate from a population with little migration is equal to the birth rate minus the growth rate; if the birth rate and growth rate can be estimated independently, their difference can be used to validate a measure of the death rate. These methods make crucial assumptions: that the reported deaths are representative of all deaths in the population; that reporting of age at death is accurate; and that net migration is zero. At best they estimate coverage only relative to an intercensal (typically a period of 10 years) average level of mortality, but evidence shows them to be an inexpensive approach to adult mortality estimation in the absence of complete civil registration. This approach offers two possible additions for specific causes. First, a question about the time of death relative to pregnancy can be asked to estimate pregnancy-related mortality ratios (panel 1 and table 2 show an example from Latin America), and second, a question about whether death resulted from injury can be included. Households reporting a death, or a sample of them, can be followed-up after the census to do a verbal autopsy (panel 2) to identify the cause of death as precisely as possible. These methods for assessment of coverage can also help to estimate the completeness of civil registration data of uncertain quality; after appropriate correction, age-specific mortality rates can then be estimated.

The population census can also contribute to estimates of adult mortality by including simple questions on survival of parents of each respondent. Brass first developed an approach to estimate adult mortality from survey information about survival of parents; the method has been refined since. The basic idea is that the proportion of respondents of a specific age whose mother

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### Key messages

- The complete registration of births and deaths with accurate ascertainment of cause of death—products of a fully functional civil registration system, and an essential component of any health information system—is inadequate in many developing countries.
- Interim measures developed over the past four decades have been reasonably adequate substitutes in countries without a fully functional civil registration system, with exception of the assessment of causes of deaths.
- These measures, consisting of innovative strategies both for obtaining data and for methods of assessment and analysis, should not, however, be viewed as long-term alternatives to civil registration, but rather as being complementary to such systems.
- International agencies should maintain their support for coordinated data collection and sharing activities and for specialised training, while increasing efforts to achieve a fully functional civil registration system.
- More intensive and better funded research programmes than we have at present are urgently needed to improve and refine the methods of analysis for converting incomplete or indirect information about mortality and causes of death into valid measures of population health for policymaking and planning.

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### Table 1: Contributions of alternative approaches to measurement of key population health indicators

<table>
<thead>
<tr>
<th>Level of estimate</th>
<th>Civil registration system</th>
<th>Demographic surveillance sites</th>
<th>Sample registration systems</th>
<th>Population censuses</th>
<th>Household sample surveys</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Births</strong></td>
<td><strong>National</strong> Yes</td>
<td>No</td>
<td>Yes</td>
<td>Maybe</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><strong>Differentials</strong> Yes</td>
<td>Limited</td>
<td>Limited</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Child mortality</strong></td>
<td><strong>National</strong> Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><strong>Differentials</strong> Yes</td>
<td>Limited</td>
<td>Limited</td>
<td>Yes</td>
<td>Yes†</td>
</tr>
<tr>
<td><strong>Adult mortality</strong></td>
<td><strong>National</strong> Yes</td>
<td>No</td>
<td>Yes</td>
<td>Maybe</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td><strong>Differentials</strong> Yes</td>
<td>Limited</td>
<td>Limited</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cause of death</strong></td>
<td><strong>All</strong> Yes</td>
<td>Yes§</td>
<td>Yes§</td>
<td>Maybe</td>
<td>Yes§</td>
</tr>
</tbody>
</table>

*With assessment and possible adjustment; methods do not always work. †For a recent period by indirect methods. §For an intercensal period. ¶Methods measuring parental survival or sibling history. **With verbal autopsy. ***For child deaths identified by a full birth history.

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or father has died will vary with the level of adult mortality. This method is attractive because the basic questions are so simple and can also be included in household surveys, but the estimates obtained are of average mortality over a long period in the past, and seem to underestimate overall mortality somewhat.13

Sample registration systems
Some countries have responded to inadequate civil registration by the implementation of registration of a sample of births and deaths. The best known, and probably most successful, example of this approach is the Indian Sample Registration System,21 which started in 1964 and expanded to cover the whole country by 1970. In sample areas (about 7000 areas covering nearly 1% of the population), a part-time registrar records births and deaths continuously; additionally, twice a year, an independent survey team interviews all sample households, asking specifically about births and deaths in the previous 6 months. The two sets of events are then matched, and any discrepancies are investigated. The final count of events is the total of matched events plus those recorded only by the registrar plus those recorded only by the household interview. Independent evaluation suggests that the system captures about 85% of deaths.22,23 Panel 3 reviews developments in the Indian Sample Registration System and in a broadly similar system (of disease surveillance points) in China. Although this system has been successful in India, sample registration systems need sophisticated administration, sustainable resources, and like civil registration systems, they are susceptible to disruption by civil unrest.

Demographic surveillance sites
Another approach, similar to sample registration systems in terms of actively identifying events through regular household visits, but different in being limited to a defined geographic region and thus not necessarily representative of the national population, is the demographic surveillance site. The INDEPTH Network provides a coordination role across 37 such sites, 26 of which are in Africa, in 19 countries. The exact process of surveillance varies substantially from yearly household surveys done by interviewers to fortnightly visits to each household by local registrars. The aim is to ensure that all vital events in the period since the last visit are recorded. The population under surveillance is usually 50 000–200 000, although methods are available to establish the appropriate sample size.34 The
best known (and longest-lived) example of a demographic surveillance system is the Matlab site in Bangladesh. The main limitation of data from such surveillance is that they are restricted to small geographic areas, which are usually intervention trial sites with small populations, and numbers cannot be generalised reliably. Panel 4 and figure 2 show how demographic surveillance systems have contributed to health planning in Ghana.

**Demographic household surveys**

One of the most important developments of the past 30 years in understanding levels and trends in worldwide child mortality has been the internationally coordinated demographic household survey programme. The first such programme was the World Fertility Survey implemented in the 1970s and early 1980s with surveys in more than 40 countries, and has since been followed by the Demographic and Health Surveys (DHS) and UNICEF’s Multiple Indicator Cluster Survey programmes. Almost all countries with inadequate civil registration have done sample surveys of households in one or other of these programmes, which provide most of what we know about levels and trends in infant and child mortality in such countries. A key strength of the DHS programme has been rapid publication of results and access to data for individuals, which has enabled a wide range of analyses.

The main innovation of these surveys is the widespread use of a full birth history, whereby every sampled woman (in some settings limited to ever-married women only) is asked about the date of birth of each of her liveborn children, whether the child is still alive, and if not, how old the child was at death. These data permit the calculation of both fertility rates (for which adjustment has been made. Reported births must also be checked; in this case reporting of births was close to correct. No formal methods exist to assess the reporting of pregnancy-related deaths, but the proportion of all deaths of women that were pregnancy-related can be expected to follow a broadly U-shaped pattern with age, and this pattern was duly seen in Honduras.

These surveys typically include small but nationally representative samples of 3000–30,000 households (although three such surveys in India have included about 90,000 households). The small samples allow for careful monitoring of the quality of data, but restrict the ability to make precise estimates of some indicators for subnational areas or population subgroups; for example, even the very large samples in India were unable to quantify trends in maternal mortality between 1992–93 and 2006 reliably because of a large margin of error.

Data from these surveys are useful for assessment of the performance of civil registration systems. Figure 3 shows a comparison of the estimates of under-5 child mortality from two household surveys in Azerbaijan to estimates from civil registration, clearly showing the high level of under-reporting of deaths in the civil registration system.

In 1991, DHS introduced a maternal mortality module into selected surveys. This module collected a complete history of siblings (ie, for each sibling born of the same mother, the age of those still alive and the year and age at death for those that have died), essentially a complete birth history of the respondent’s mother. For sisters who had died between the ages of 15 and 49 years, further questions on the timing of death relative to pregnancy were asked to identify pregnancy-related deaths. The sibling history theoretically permits the estimation of overall mortality for men and women from birth to age 50 years and the estimation of pregnancy-related mortality ratios. Analysis of DHS sibling histories has suggested that overall mortality and pregnancy-related mortality ratios were generally under-estimated.

### Panel 1: Estimation of maternal mortality from a census in Honduras

Maternal mortality was identified as a priority for intervention by the government of Honduras in 1992, and several exercises to measure the maternal mortality ratio have been undertaken. The 2002 census of Honduras included questions about deaths in each household in 2001, and recorded the age and sex of each deceased person. Additional questions were included for the deaths of women of reproductive age, as to whether the woman was pregnant at the time of death, died during delivery, or died in the 2 months immediately after delivery. Using such data to estimate maternal mortality ratios needs three pieces of information, each of which must be checked for accuracy, and an assumption. The three pieces of information are accurate counts of deaths of women of reproductive age, of deaths that were pregnancy-related, and of births. The assumption is that deaths that are pregnancy-related are not always recorded as such (eg, the respondent might not have known that the woman in question was pregnant) and that the magnitude of the error is about equal to the proportion of pregnancy-related deaths that are actually maternal deaths according to ICD-10. Each piece of information must be checked for accuracy; unfortunately not much can be done to check the assumption.

Experience with census questions about household deaths suggests a probability of omission of deaths. Assessment of the quality of the data is therefore essential, as is adjustment for omission, if necessary. The female deaths by age reported for 2001 were compared with population change between the 1992 and 2002 censuses using two methods, the general growth balance method and the synthetic extinct generations method. These methods suggested a substantial under-reporting of household deaths, for which adjustment has been made. Reported births must also be checked; in this case reporting of births was close to correct. No formal methods exist to assess the reporting of pregnancy-related deaths, but the proportion of all deaths of women that were pregnancy-related can be expected to follow a broadly U-shaped pattern with age, and this pattern was duly seen in Honduras.

<table>
<thead>
<tr>
<th>Deaths of women aged 15–49 years</th>
<th>1753</th>
<th>0.587</th>
<th>2987</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of those deaths that were pregnancy-related</td>
<td>10%</td>
<td>1.0</td>
<td>10%</td>
</tr>
<tr>
<td>Births</td>
<td>170 389</td>
<td>0.596</td>
<td>169 707</td>
</tr>
<tr>
<td>Estimated maternal mortality ratio</td>
<td>107</td>
<td>n/a</td>
<td>183</td>
</tr>
</tbody>
</table>

Table 2: Maternal mortality in Honduras in 2001 recorded in the 2002 Census
Series

Panel 2: Verbal autopsy methods

Demands have increased for robust, comparable data for mortality for evidence-based resource allocation and for assessment of public-health interventions in middle-income and low-income countries. Since a functional civil registration system capable of giving robust estimates of cause-specific mortality rates does not exist in these settings, assessment of causes of death needs to be based on an alternative approach. One approach used in many settings is the verbal autopsy, whereby family members of an identified deceased person provide information about the circumstances surrounding their death. This information can consist of a check list of symptoms, a narrative description of the process leading up to death, cause of death as indicated at a health facility, or any combination of these methods. However, the heterogeneity of verbal autopsy tools and differences in operating procedures for verbal autopsy render comparisons of data between demographic surveillance sites impossible. The need for standard verbal autopsy tools and procedures for international use has been recognised since the introduction of this method.

Verbal autopsy methods have undergone several important developments. First, WHO in collaboration with partners has made the first step toward harmonising the cause-specific data for mortality obtained by verbal autopsy by proposing standard questionnaires for adult, child, and neonatal deaths and a core cause-of-death tabulation list that includes the categories of disease that are important worldwide and have a reasonable probability of being ascertained by verbal autopsy. The validity of proposed standard verbal autopsy instruments will probably be similar to those that have already been validated in similar settings. However, further validation of these instruments in different settings will be needed. Meanwhile, application of a standard verbal autopsy questionnaire and core cause-of-death list should be advocated by international and national organisations to improve comparisons of data for verbal autopsy between sites. Second, an innovative technique to assign causes of death has been developed. Estimates from this method do not need review by physicians, expert algorithms, or parametric statistical modelling, which can substantially enhance the ability to compare or reproduce the results from verbal autopsies. Further work on the procedures to ascertain causes of death from verbal autopsy is needed to improve consistency and sustainability of verbal autopsy systems. The proliferation of household surveys and the 2010 round of censuses will provide opportunities to implement verbal autopsy modules and to increase information about cause of death.

However, several operational and technical issues need to be assessed before recommending verbal autopsy modules widely in household surveys or censuses. Operationally, debate continues about whether verbal autopsy modules should be integrated in surveys or done separately after identifying deaths in the household. A trade-off is obvious between the burden imposed on respondents, when integrated, and the higher chance of loss to follow-up if implemented separately. Verbal autopsy also needs special training of people to interview and code the responses. Cost-effectiveness of different options should be carefully assessed. We also need to know how large the sample size would need to be to derive meaningful distribution of cause of death by age and sex for main causes; how large the sample size would need to be to monitor significant changes in deaths from specific causes; and what would be done if the sample was small. WHO is working with partners to develop guidelines for these issues to inform potential users of verbal autopsy modules and to enhance the consistency of cause-of-death information derived from verbal autopsy tools, and allow comparisons to be made between countries.

Potential uses of incomplete data

Although civil registration systems in developing countries frequently fail to record all events, incomplete data that are available can still be used (although it is often not tabulated because of concerns about quality). We have discussed above the analytic methods for assessing the completeness of registration of adult deaths; if reporting is complete enough for the recorded deaths to be plausibly representative of all deaths in terms of age distribution (Preston suggests a minimum level of completeness of around 60%) the data can be adjusted to give largely unbiased estimates of adult mortality. About 40 developing countries might have sufficiently complete data to make reliable estimates. Other examples of uses for incomplete data exist also. Civil registration is usually more complete in cities, especially capital cities, of developing countries than it is in rural areas. Analysts have taken advantage of such data to examine issues such as seasonal variation in mortality and the effects of HIV on mortality.

Incomplete information about cause of death from hospital records provides an alternative approach to the use of verbal autopsy; even though recording of cause of death in hospitals is far from perfect in countries with inadequate statistical systems, the recorded cause has substantial information content, especially if assessed in combination with case notes. However, deaths occurring in hospitals (or other facilities in which cause of death can be established with some degree of validity) cannot be regarded as a random sample of all deaths in a population. They will be biased by various characteristics, including the underlying cause of death. However, if the selection process can be satisfactorily modelled, the recorded distribution can be weighted appropriately to calculate a distribution representative of the whole population. Information from hospital records also gives valuable insights into both underlying or multiple causes of death, which is increasingly relevant in view of the rising proportion of non-communicable diseases worldwide.

Modelling

Models of age patterns of mortality have a long history. The potential value of such models rests on the empirical
observation that human mortality systematically varies with age: it is high in infancy, drops to a minimum around age 10 years, and then increases exponentially with age. This regular pattern has given rise to the development of many model life-table systems, mostly on the basis of the historical experience of countries that now have low mortality.\(^5\)\(^4\)\(^1\) One contemporary problem with such models is the difficulty in incorporating excess AIDS mortality in a simple way.

Models have also been developed for calculating distributions of deaths by cause. Initially, simple linear models were developed to predict the relationship between overall mortality and structure of deaths by cause.\(^4\)\(^5\)\(^6\) Subsequent compositional models that allowed for prediction of non-linear relationships,\(^6\)\(^7\)\(^8\) have further refined the estimation of the distributions by cause of death of children aged under 5 years.\(^9\)\(^10\) Disease models have also been developed to predict mortality from cancer dependent on its incidence.\(^5\)\(^3\)\(^4\) Although models are useful to assess the plausibility of local data from verbal autopsy or civil registration, models are neither a substitute for reliable directly-obtained data for mortality nor are they useful for monitoring trends over time.\(^7\) Methods of estimating the quality of data for cause of death exist, with reallocation algorithms applied to senility and ill-defined causes, including vague diagnoses of cancer and cardiovascular diseases.\(^11\) and police records have been used to correct vital registration data for traffic crashes. The joint application of disease modelling with prudent interpretation of locally available data can yield useful estimates of cause-of-death patterns for a population.\(^11\)\(^16\)

**Complementary methods for obtaining data**

The discussion of interim measures should not be interpreted to mean that a fully developed health information system can rely exclusively on civil registration data combined with denominators from censuses or population registers. Such data provide an essential basis for descriptive epidemiology, but need supplementation for in-depth analyses and also need periodic validation.

A particular shortcoming of civil registration data is the absence of good socioeconomic information. Linking of death records to earlier survey information, as in the National Death Index in the USA,\(^7\) has proved especially useful by providing characteristics of
Individuals for several years before their death, thus converting cross-sectional data into prospective data.

Also missing from civil registration data is information about risk factors and the health status of living people, such as is provided by health examination surveys such as the National Health and Nutrition Examination Survey or interview surveys such as the National Health Interview Survey in the USA. Thus, survey programmes are an essential component of fully developed systems, and they provide interim mechanisms for countries with inadequate systems.

**What interim methods cannot do**

Inevitably, interim solutions described here cannot fulfil all functions. By their nature, interim approaches generally rely on retrospective reports of events; they are thus prone to selection bias. For example, both full and summary birth histories exclude births and deaths of children of women who have died. Any strong association between the risk of death of the child and that of the mother will bias estimates of child mortality and distort associations with predictor variables. Similarly, retrospective reports cannot give timely warning of mortality crises: by the time a census or survey has been done, the crisis, be it a famine or genocide, will usually have happened a long time ago. Sample registration might identify a crisis, but the nature of the system of obtaining and checking data, such as that used by the Indian Sample Registration System delays access to timely results. Sample sites might entirely miss health events because of the sampling design or choice of sample population. A demographic surveillance site might provide useful information (an example is the analysis of the demographic effects of civil war in Bangladesh in 1971), but generally inadequate access to data and poor representation of a population by such data are

**Panel 4: Demographic surveillance systems in practice in Ghana**

Demographic surveillance systems continuously record longitudinal demographic data, usually within small geographically defined populations. These systems start with an initial census to define the baseline denominator population and thereafter continuously monitor this population at well defined periods of time to record changes or events that take place in the initial population. Although the length of follow-up varies, three times a year is typical. During these routine visits, vital events such as births, deaths, migrations, and in some cases pregnancies are registered and monitored. Deaths recorded by field workers are followed up with verbal autopsy interviews using standardised interview protocols.

In Ghana, three demographic surveillance sites are strategically located in the north (Navrongo), the central belt (Kintampo), and the coast (Dodowa) (figure 2). The three sites cover entire districts with a total population of nearly 400,000. Together, these sites provide representation of the main ecological divisions of the country. Data gathered at these sites could therefore be said to fairly represent the main ecological or geographical zones of Ghana. All three sites are administered by the Ghana Health Service and work closely with the respective district health services. The three sites are members of the INDEPTH Network and thus collaborate closely with one another in technology sharing and transfer, including strengthening or building of capacity.

Coverage of vital events in the demographic surveillance areas is almost 100% because all households are visited at least three times a year and births, deaths, and migration events are recorded. Verbal autopsy to ascertain cause of death is done for all deaths reported. Other demographic or health-related data such as pregnancies are also recorded. Demographic surveillance data therefore constitute one of the most reliable and perhaps, in the current circumstance of low civil registration coverage, the most important source of health information in Ghana. The Ghana Health Service launched a programme in 2004 for transforming clinic-based primary health care and reproductive health services to community-based health services based on results of an experiment done by the Navrongo Health Research Centre at the Navrongo site. Known as the Community-based Health Planning and Service, the programme promotes the idea that communities can be active participants in the provision of their own health care. It places community health officers and volunteers in all 138 districts of Ghana to provide basic health services to all communities. The community health officers and volunteers live and work in the communities, providing door-to-door services to individuals within households.

For more on the INDEPTH Network see http://www.indepth-network.org

For more on the Ghana Community-based Health Planning and Service see http://www.ghana-chps.org

![Figure 2: Demographic surveillance sites in Ghana](image-url)
drawbacks. Continuous monitoring of vital events with medical certification of deaths through a civil registration system is the only satisfactory mechanism.

Conclusions and recommendations
The interim methods for estimation of vital statistics discussed here have largely been developed in the past four decades as cost-effective alternatives for deriving demographic estimates in the absence of civil registration. Substantial progress with these methods means that we now know much more than before about the demography and descriptive epidemiology of populations across the world. Necessity has truly been the mother of invention for this subject, since much of this achievement has been in response to the absence in many poor countries of the optimum information source, namely a fully functioning civil registration system.

However, these methods are not alternatives to each other, and should not be viewed as such, but as complementary with powerful synergistic potential. Although they are substitutes and interim measures in the world’s poor countries, such surveys and methods also continue to have a valuable role in providing a range of information that is complementary to that of civil registration in those countries fortunate enough to have fully developed statistical systems and they can also be used as independent validation and quality controls for civil registration systems. Thus, state-of-the-art health information systems consist of two complementary parts, first a universal and effective civil registration system, and second, a variable range of information from censuses and sample surveys in addition to civil registration systems.

Most of the world’s poor countries already have the second part in place today through external technical assistance and funding; in fact, this part of the system is the more intellectually advanced and technically difficult of the two. These countries need investment only in the basic, less demanding part (civil registration) to rapidly achieve health information equality with the most advanced countries in the world. Such equality is a substantial development that is worth the effort. The development of these data sources and application of methods of assessment and estimation has resulted in a substantial body of workers around the world, in government, academia and the private sector, with highly relevant skills and experience who are able to assist countries now seeking to improve or build their civil registration systems. The existence of this human capital provides a unique opportunity for the world’s poorest countries to leapfrog to a position of technological equivalence with the most developed countries in terms of their health and demographic information systems.

The incentive to complete such a system is large for both poor countries and the world’s development agencies, because having both civil registration and complementary systems running together, as the world’s developed countries do, results in great synergy. Thus, the crucial decision that we advocate is not investment in civil registration systems around the world so that all alternative systems can be abandoned as mere interim measures that will no longer be needed. On the contrary, the technical capacity built in the past several decades to create and refine these alternative systems will be crucial for establishing, improving, continually monitoring, and adding value to civil registration systems in poor countries. Groups that have invested in making the alternative systems work should be asked for support and leadership for building these civil registration systems, which will complete the information goals they have been striving towards.

International organisations need to maintain a leading role in supporting coordinated survey programmes such as DHS and in both encouraging countries to include relevant questions in their censuses and surveys and in supporting those countries with analysis of obtained data. A stronger research effort than at present is needed to improve methods of estimating mortality, and the ascertainment of cause of death by standardised verbal autopsy instruments or by incomplete information about cause of death from health facilities. Despite the need for such progress, for many countries we now have enough information to be reasonably confident about mortality estimates in populations, or at least about the probable extent of uncertainty in the estimates. We might all take solace in the words of Major Greenwood, who commented more than half a century ago that: “making the best the enemy of the good is a sure way to hinder any statistical progress. The scientific purist who will wait for medical statistics until they are nosologically exact, is no wiser than Horace’s rustic waiting for the river to flow away”.
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In November, 2006, a 64-year-old woman was referred to our clinic. She was suspected to have arthritis caused by systemic lupus erythematosus: she had pain in both hands, and antinuclear antibody had been detected by a blood test. The pain had begun 3 months previously, and worsened steadily; her weight had fallen by 7 kg, and she reported excessive fatigue. She had smoked around 20 cigarettes a day, for 40 years. Her past medical history was otherwise unremarkable. Naproxen, morphine, gabapentin, and prednisolone had not reduced the pain.

The patient’s palms were red and warm. The skin was dry and peeling (figure). There was no synovitis or limitation of movement. Neurological examination showed mechanical allodynia, hypoesthesia, and vibration and proprioception deficits in both hands. Coordination was much reduced when the patient’s eyes were closed—which, in the absence of cerebellar signs, signified sensory ataxia. No other abnormalities were found on examination. Results of a full blood count, general biochemistry screen, and thyroid function tests were normal, as were serum glucose, vitamin B12, and folate. Tests for HIV and syphilis were negative. The ESR and concentration of C-reactive protein were slightly raised, at 29 mm/h and 10.9 mg/L respectively. Antinuclear antibody was found at a titre of >1:160, but antibodies to DNA and extractable nuclear antigens were not found. Nerve conduction studies showed absent sensory conduction in hands and feet, and normal motor conduction. MRI of the head and neck showed nothing of note. The patient refused a lumbar puncture. Chest radiography showed no abnormality, but in view of the patient’s neurological symptoms, weight loss, and smoking history, CT of the chest was done. A mass measuring 3·0×1·5 cm, and compressing the inferior pulmonary vein, was found in the left lung base. Suspecting a paraneoplastic syndrome, we requested antineuronal antibody titres. Anti-Hu antibody was detected by immunohistochemistry at a titre of >1:1000, a finding confirmed by western blotting. Histopathological examination of an endobronchial biopsy sample was diagnostic for small-cell lung cancer. PET showed that the malignancy was confined to the chest. The patient was referred to the oncology department of her community hospital. When we last saw her, in December, 2006, she had developed sensory symptoms in her feet.

Paraneoplastic neurological syndromes affect only a small minority of patients with solid malignant tumours. However, when they occur, they are detected before the cancer in 60–80% of patients. Most are thought to arise when tumour cells express neuronal antigen, provoking an autoimmune response that damages nerves. Subacute sensory neuronopathy is paraneoplastic in only around 20% of cases—but, when paraneoplastic, is strongly associated with lung cancer, and particularly with small-cell lung cancer. The first symptoms are usually pain and paraesthesia in the hands and feet. However, the disease can also present with autonomic neuropathy, including vasomotor and sudomotor dysfunction, which, in our patient, seems to have caused red palms and dry skin. Subacute sensory neuropathy usually evolves rapidly, leading to severe impairment of all sensory modalities within months. CSF examination is diagnostically unhelpful, but nerve conduction studies characteristically show absent or greatly reduced sensory-nerve action potentials. Moreover, the detection of antibodies to Hu antigens, which are nuclear proteins normally expressed by all neurons, has a specificity of 99% and sensitivity of 82% for paraneoplastic sensory neuropathy, when the diagnosis is clinically suspected. Antinuclear antibodies are found in up to 48% of patients with paraneoplastic syndrome and antibodies to Hu antigens; this finding can mislead the clinician to search for connective-tissue disease, as happened here. Treatment with steroids, intravenous immunoglobulins, or plasma exchange rarely helps patients with paraneoplastic subacute sensory neuropathy. The best treatment is to find and treat the cancer.

References