

feasibility of this strategy. How can the use of a polypill be implemented in a broad population? What is the full safety profile (there were 3–8% of patients who had increases in creatinine and potassium and in liver function tests; what adjustments need to be made to those patients?). Do they stop the polypill if one component causes a side-effect? How does the doctor decide which component caused the side-effect? Second, we would also like to have a large outcomes trial, to document a reduction in death, myocardial infarction, and stroke with the polypill approach compared with current practice.

Third, there is the issue of dose, which is a fascinating difference from current practice. The Polycap had just one dose (generally a moderate dose) of each agent. Currently for combination pills, regulatory authorities require that the pill be available in every dose combination of each drug, so the combination pill would not limit treatment. However, this approach would obviously not be feasible with a pill with five or six components and each having two to four doses (which would lead to more than a hundred strengths of the polypill). Thus what is designed to be a simple pill would turn into a complicated prescribing morass. It might be feasible to consider having two or three broad strengths with some different doses of some components (eg, the antihypertensives) or there could be versions with only some components of the polypill that would, for example, have fewer antihypertensive drugs. That approach might help when treating a patient with only single risk factors (eg, a smoker without high blood pressure). Should such a patient be put on three antihypertensives, and thus have the risk of angio-oedema, glucose intolerance, or bradycardia?

A final challenge: would the availability of a single magic bullet for the prevention of heart disease lead people to abandon exercise and appropriate diet? Would this make two of the major root causes of heart disease worse? Hopefully not, but the medical profession would need to help ensure that this would not happen.

Where would this polypill fit into current medical practice? The major appeal is its simplicity and (presumed) low cost, which could improve compliance.<sup>3</sup> Such appeal could have broad applicability in areas of the world with less access to medical treatment, where just one or two interactions with medical professionals could be the start of treatment that could lead to long-term cardiovascular prevention. But the polypill could also fit well into more modern medical systems, in which large proportions of patients with risk factors are untreated.<sup>4</sup> If all these patients knew they could simply take their polypill, they might be more receptive to it—and as such vastly broaden the number of patients who might benefit from drugs that had been proven in multiple trials to reduce cardiovascular disease and mortality. Although TIPS does not provide all the answers, the study does take a first and crucial step forward and raises hope that, in conjunction with other global efforts to improve diet and exercise, the polypill could one day substantially reduce the burden of cardiovascular disease in the world.

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## Should the CD4 threshold for starting ART be raised?

Since the development of combination antiretroviral therapy (ART) for HIV in the mid-1990s, changes in recommendations on when to start treatment in high-income countries have been likened to a swinging pendulum.<sup>1–3</sup> After the dismal prognosis for patients in the pre-ART era,

the initial approach of early aggressive therapy was based on enthusiasm derived from theoretical considerations.<sup>4</sup> However, subsequent data from observational studies and short-term clinical trials revealed unexpected long-term metabolic and cardiovascular toxicities, leading

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to a shift in expert opinion toward a more cautious approach.<sup>3</sup> Recommendations to date, however, have largely remained uninformed by data from randomised trials with clinical endpoints.

Current British and American guidelines recommend that, in the absence of an AIDS-defining illness, ART should be started in patients with blood CD4 cell counts in the range 200–350 cells per  $\mu\text{L}$ .<sup>5,6</sup> With the development of treatment regimens with lower toxicity and increasing evidence that HIV-associated morbidity and mortality develop at CD4 cell counts substantially higher than 200 cells per  $\mu\text{L}$ ,<sup>7</sup> it might be time for the pendulum to swing once more towards earlier treatment.

In *The Lancet* today, the When To Start Consortium presents an analysis of data from over 45 000 patients from 18 observational HIV cohorts in Europe and North America.<sup>7</sup> Frequency of death, or combined AIDS and death, in patients receiving and not receiving ART was used to identify a minimum threshold of 350 cells per  $\mu\text{L}$  for starting ART. The validity of this recommendation is greatly strengthened by the large numbers of patients, diversity of cohorts, the ability to compare event frequencies between narrow overlapping strata of CD4 cell counts and, crucially, the adjustment for lead-time bias.

Observational data can be subject to unrecognised confounders, and the analysis did not include non-fatal non-AIDS events or data on quality of life or adherence. At higher CD4 cell counts, differences in non-AIDS morbidity between strata for CD4 cells might be important, as shown in a small subgroup analysis from the Strategies for Management of Antiretroviral Therapy (SMART) study.<sup>8</sup> In that study, ART-naïve individuals with CD4 cell counts higher than 350 cells per  $\mu\text{L}$  were randomly assigned either to receive immediate ART or to defer ART until counts were less than 250 cells per  $\mu\text{L}$ . Those who deferred treatment had a far higher rate of major morbidity and all-cause mortality than did those treated immediately (4.9 vs 1.0 events, both per 100 person-years, respectively). These data suggest that, when taking into account serious non-AIDS events, the potential benefit to be derived from earlier initiation of ART might be even greater than that suggested by the When To Start Consortium.

The data presented by the When To Start Consortium support a shift in recommendations towards initiation of ART at a minimum CD4 cell-count threshold of 350 cells per  $\mu\text{L}$ .<sup>7</sup> However, while acknowledging the

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strength of this analysis, these observational data are not definitive. Randomised trials are needed in which more varied data are collected. At high CD4 cell counts, differences in absolute risk of AIDS and death between early and deferred ART are small, and uncertainty about the risk to benefit ratio remains. Even when benefits outweigh risks, cost-effectiveness is unclear. Data are needed on serious complications of ART that might negate the benefits, such as cardiovascular, renal, and hepatic disease. Furthermore, the effect on the quality of life should be assessed. A large randomised study assessing such variables, the Strategic Timing of Antiretroviral Treatment (START) study, is due to begin this year.<sup>9</sup>

The data in the When To Start Consortium study were from cohorts in industrialised countries and cannot be assumed to be directly applicable to patients in all settings. Mortality rates and the range of morbidity differ between cohorts in industrialised countries and resource-limited settings. Data from South Africa, for example, indicate that unusually high rates of AIDS and death occur in patients with CD4 cell counts in the range 200–350 cells per  $\mu\text{L}$ .<sup>10</sup> Early mortality in patients receiving ART in sub-Saharan Africa is also substantially greater than in those treated in high-income countries.<sup>11</sup> Moreover, the range of ART drugs available and cost-effectiveness considerations can be more restrictive in developing countries.

Thus, when considering both high-income and resource-limited settings, the question of when to

start ART might have more than one right answer. WHO guidelines for resource-limited settings currently recommend initiation of ART before blood CD4 cell counts fall below 200 cells per  $\mu\text{L}$  with an upper threshold of 350 cells per  $\mu\text{L}$ .<sup>12</sup> To inform these recommendations, randomised trials should include patients living in resource-limited settings.

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## Prevention of diabetic retinopathy

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Most patients with diabetes develop retinopathy if they live long enough; 50% of patients with type 1 diabetes and 30% of those with type 2 diabetes can expect to develop sight-threatening retinopathy in their lifetime and need intervention to reduce the risk of vision loss.<sup>1</sup> Good control of blood glucose and blood pressure greatly reduces this risk.<sup>2</sup> Further reduction of the retinopathy risk with drug therapy is a desirable goal, and several classes of molecules have been tested for this effect.

Aldose reductase inhibitors were promising as inhibitors of diabetic retinopathy; however, clinical trials were disappointing.<sup>3</sup> Protein kinase-C inhibitors were also thought to be beneficial, but again, clinical trials dashed these hopes. Ruboxistaurin did not slow the development of clinically significant diabetic oedema,<sup>4</sup> although it may have some beneficial effect on vision.<sup>5</sup> Angiotensin-converting-enzyme inhibitors slow the development of diabetic retinopathy<sup>6</sup> and angiotensin-receptor blockers also retard the development of retinopathy,<sup>7</sup> although the effect is not dramatic.

In *The Lancet* today, Christos Haritoglou and co-workers<sup>8</sup> tested whether calcium dobesilate would decrease the incidence of diabetic macular oedema, in the CALDIRET study. Diabetic macular oedema is an appropriate endpoint because it is the most common cause of diabetic blindness and the most common form of sight-threatening retinopathy. This randomised, double-blind, placebo-controlled study included 635 patients with non-proliferative diabetic retinopathy who were followed up over 5 years. 28–35% of the group developed diabetic macular oedema during the trial, which is within the expected range<sup>1</sup> and high enough to allow meaningful assessment of the effectiveness of the drug. The outcome was that calcium dobesilate was not different from placebo in retarding the progression from non-proliferative diabetic retinopathy to clinically significant diabetic macular oedema. This result is a disappointment, especially in view of previous publications that proposed calcium dobesilate for the treatment of diabetic retinopathy,<sup>9</sup> even though CALDIRET used a slightly higher dose of calcium