to different ways of framing decisions on rationing. From this flowed recognition of the importance of "ensuring that the processes by which decisions are reached have legitimacy" and that there should be "accountability for reasonableness."[6]

It remains to be seen how this new strategic emphasis will work out. There remains, however, the problem—already touched on—of how macrodecisions about rationing are translated into microdecisions at the delivery end of health care. Economic analysis depends on information about effectiveness produced by clinical trials. And the limitation of most clinical trials is that "they fail to reveal the potentially complex mixture of substantial benefits for some, little benefit for many, and harm for a few."[7] This is why systems level rationing decisions almost invariably—across different healthcare systems—allow for clinical discretion in the interpretation of such guidance. But this leaves us with the so far unanswered question of how, and to whom,

individual clinicians should be held accountable for "reasonableness" in the exercise of their discretion.

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Highly active antiretroviral therapy

Cardiovascular risk needs to be assessed before starting treatment

In the industrialised world the availability of highly active antiretroviral treatment (HAART) for advanced HIV-1 disease has dramatically improved patients' life expectancy.[1] However, an unfailing lifelong commitment to antiviral drugs is expected. Furthermore, recent evidence is mounting that cardiovascular and cerebrovascular accidents might seriously impair the health of infected individuals,[2] and the resulting morbidity and mortality have put an end to the unlimited optimism that was associated with the beginning of the HAART era. Here we look at the importance of assessing and targeting the risk of cardiovascular disease before starting HAART and consider what effect this risk has on determining the best time to start treatment.

For people infected with HIV-1, HAART may substantially increase the risk of cardiovascular mortality compared with non-infected individuals or with people infected with HIV who are not yet taking HAART.[3] HAART is associated with known cardiovascular risk factors such as increased plasma concentrations of triglycerides, total cholesterol, possibly hypertension,[4] and increased insulin resistance. In addition, HAART induces endothelial dysfunction, which is known to increase the risk of coronary heart disease.[5]

The medical management of cardiovascular risk factors in patients on HAART gives rise to other problems related to HIV and HAART, such as an additional pill burden, which may impair adherence and lead to increased resistance.[6] This highlights the importance for such patients of reducing risk through changes in lifestyle, such as smoking cessation, salt restriction, and physical activity.

A proper assessment of current cardiovascular risk factors in HIV-1 infected individuals is of critical importance in order to implement strategies to reduce risk. Someone with HIV-1 infection should receive a cardiovascular risk profile as soon as possible and certainly before treatment is started, to inform timing and choice of regimen for HAART. The score most

applicable for this purpose is the Framingham risk score corresponding to known cardiovascular risk factors.[7] HAART may increase this score[8] through alterations in triglycerides, total cholesterol, high density lipoprotein, and possibly through the emergence of hypertension.[4] Currently the decision to start HAART is based on CD4T lymphocyte cell counts. Antiretroviral treatment will be started if the cell count drops below 350×10^6l cells (Yeni P, keynote lecture, 7th International Congress on Drug Therapy and HIV Infection, Glasgow, 14-18 November 2004).

A concentration of 200×10^6l cells is considered as the lower limit for starting HAART, since below this threshold the chances of developing an AIDS defining illness increase dramatically.[9] Potentially, however, a considerable time span exists between 350×10^6l cells and 200×10^6l cells—given an average viral load, this could easily be two to five years.[10]

Strong efforts need to be made during the individual's pre-HAART period to reduce cardiovascular risk factors, whereby selecting the patients most likely to benefit from risk reduction strategies is essential. When the Framingham risk scale is used, a score of 23 for women and 15 for men corresponds with a 20% risk over 10 years of developing coronary heart disease.[7 11] In this particular population, lifestyle changes (and eventually lipid lowering drugs) could substantially reduce the risk of coronary heart disease,[11 12] but it has to be borne in mind that the cumulative risk of acquiring an AIDS defining event does not increase if HAART is postponed until a CD4T lymphocyte cell count of 200×10^6l is reached.[13] Furthermore, during the years of delay, new treatment options might come into life that carry less risk for cardiovascular disease.

The start of a HAART regimen remains a decision that implies an individual and a holistic approach. A high cardiovascular risk score warrants that treatment is delayed if needed until the lower threshold of 200×10^6l CD4T lymphocyte cells is reached. Imple-

menting cardiovascular risk reduction before the start of HAART, as well as for patients already taking HAART, deserves our attention in an era when we become more and more concerned with the long term side effects of HAART.[10]

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COX 2 inhibitors, traditional NSAIDs, and the heart

Adverse event data from clinical trials must inform decision making

These are trying times for patients with chronic musculoskeletal pain. Worrying data about the drugs they regularly use keep emerging. In September 2004 rofecoxib (Vioxx) was withdrawn by Merck after the adenomatous polyp prevention on Vioxx (APPROVe)[1] trial showed an increase in major cardiovascular events in patients with a history of colorectal adenomas who were randomised to receive Vioxx, compared with those in the placebo group. [w1] Rofecoxib had been marketed as the non-steroidal anti-inflammatory drug (NSAID) of choice because selective inhibition of the isoform 2 of the cyclo-oxygenase (COX 2) enzyme made it highly effective but free from gastrointestinal toxicity.

More unwelcome data from placebo controlled trials of rofecoxib's competitors followed: valdecoxib (Bextra, Pfizer) taken after coronary artery bypass grafting was shown to be associated with an increased incidence of cardiovascular events[2]; and the adenoma prevention with celecoxib (APC) trial[3] reported an increased risk of cardiovascular events associated with use of celecoxib (Celebrex, Pfizer), a drug known to be less selective for COX 2 than rofecoxib or valdecoxib.[4] A small increase in the risk of myocardial infarction was also observed for the highly selective lumiracoxib (Prexige, Novartis).[5] No data on the cardiovascular safety of etoricoxib (Arcoxia, MSD) from large trials have been published so far, but no news is no longer good news: patients and doctors are anxious to know whether cardiotoxicity is a class effect applicable to any COX 2 inhibitor, or even to NSAIDs in general.

In this week's *BMJ* two observational studies address this question. A retrospective cohort study (page 1370)[6]

in patients with congestive heart failure found lower mortality in patients treated with celecoxib than with rofecoxib or traditional NSAIDs. A case-control study nested in a UK general practice database (page 1366)[7] found a similar risk of myocardial infarction for celecoxib, rofecoxib, ibuprofen and naproxen, but a somewhat higher risk with diclofenac.

We believe that these results should be interpreted with caution. For example, the similar risk of myocardial infarction for naproxen and rofecoxib found in the case-control study[7] is incompatible with the trial data[8] and could be explained by confounding by indication if patients with a history of heart disease were more likely to receive naproxen than rofecoxib or other NSAIDs. The quality of the data on cardiovascular risk factors and other potential confounders was poor in both studies, and the ability to control for confounding therefore limited. For example, information on smoking was unrecorded in 13% of cases and 20% of controls in the case-control study[7] and entirely unavailable in the retrospective cohort study.[6]

What are the alternatives? We have argued that all unbiased data on serious adverse events from clinical trials should be made available to independent researchers and the public and analysed in a timely fashion.[9] Indeed, in the case of rofecoxib, cumulative meta-analysis of clinical trial data showed that an increased risk of myocardial infarction was evident from 2000 onwards.[8] Similar analyses are now required for the other COX 2 inhibitors.

P+ *Additional references w1 and w2 are on bmj.com*