Of course, there are hurdles to overcome before any serious discussion about application of this technique to human beings. Existing technology could potentially help to overcome these problems. One way to reduce regeneration time would be to commence cultivation of the tissue ex vivo in bioreactors and then implant a premature biological joint replacement. This preformed and immature joint replacement could provide limited functional loading, with further tissue stimulation provided by the recipient. However, as discussed, the amount of tissue generated in an artificial bioreactor is unlikely to be sufficient for this purpose. Additionally, bone and cartilage would require different competing environmental conditions during cultivation in vitro. Growing of chondrocytes and osteocytes together in one culture is therefore challenging and not currently technically feasible as regards potential use in a clinical setting.

Another promising approach would be to commence the entire cultivation of the joint replacement inside the patient, but to change the site of tissue growth (figure). Tissue at the size of a joint could be grown inside a muscle first and subsequently transplanted to replace the original joint. The patient could continue to use the compromised joint, while simultaneously growing the new one and taking advantage of in-vivo cultivation. In 2004, we described the cultivation of a vascularised individually customised mandible replacement in the latissimus dorsi of a man. The replacement was subsequently successfully transplanted to repair a defect after surgery for a tumour in the floor of the mouth.[8,9] In our work, the patient was used as the bioreactor or endocultivator to grow the replacement part, proving that endocultivation was feasible for large bone replacements. The cultivation of bone and cartilage together with this technique is a challenge that the multinational tissue engineering network, MyJoint, funded by the European Union, is working to overcome.[10] This study by Lee and colleagues offers new insights into in-vivo tissue engineering, especially in bioscaffold design and endogenous cell homing.

Ultimately, the optimum way to grow a biological joint replacement remains a controversy at this, the end of the Bone and Joint Decade. Although we are yet to see a biological joint replacement in man, Lee and colleagues have offered a promising insight into what might be on the horizon.

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I am the head and coordinator of the multinational tissue engineering network "MyJoint",[10] which is funded by the European Union. Several universities and biomedical institutes are working together to modify a recently established technique[8] to use patients as their own bioreactors to grow biological joint replacements.

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ART in low-resource settings: how to do more with less

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In *The Lancet* today, Margaret May and colleagues[1] report prognostic models for patients starting antiretroviral therapy in sub-Saharan Africa. The group analysed data from four large scale-up cohorts in the Southern and West African regions that participate in the International epidemiologic Databases to Evaluate AIDS (IeDEA). On the basis of identified risk factors for death, May and colleagues constructed two prognostic models: one with CD4 cell count, clinical stage, bodyweight, age, and sex; and one that replaced CD4 cell count with total lymphocyte count and haemoglobin concentration in the blood. The group concluded that both models provide similarly strong

discrimination for prediction of early mortality in patients starting antiretrovirals in sub-Saharan Africa.

May and colleagues reported that, during the first year after starting antiretrovirals, 912 (8%) of 11 153 patients died. Mortality would have been higher than that reported if complete follow-up data were available,[2] or if centres that provided antiretroviral therapy with less external support than those participating in the IeDEA network were included. The main reason for this high mortality was late presentation of patients to initial care and late start of treatment. However, even after adjustment for CD4 cell count, death rates in patients on antiretrovirals are much higher in sub-Saharan Africa than they are in industrialised countries.[3] The scarcity of diagnostic facilities and treatment options for opportunistic infections are the major contributing factors to this high mortality. Conversely, the roles of immune reconstitution inflammatory syndrome and toxic effects of antiretroviral therapy remain to be established.[4] Unfortunately, since the introduction of antiretroviral therapy in sub-Saharan Africa, no well-designed post-mortem investigation has been done to guide us about predominant causes of death.

May and colleagues reported biological variables as prognostic indicators; although in sub-Saharan Africa socioeconomic factors are important determinants of survival,[5] such as the ability to pay for food, drugs, investigations, transport, and support of a family member during their time in hospital.

May and colleagues[1] mainly discuss mortality while patients are taking antiretrovirals, but an unacceptably high pretreatment mortality in sub-Saharan Africa remains. In countries such as the Democratic Republic of the Congo, most antiretroviral programmes have stopped enrolling new patients,[6] and new slots for treatment only become available when a patient dies or is transferred out. Waiting lists for starting antiretrovirals have been reintroduced, leading to increased pretreatment mortality.[7]

There is a widening gap between what WHO recommends for treatment of patients with HIV infections in low-income countries[8] and what is available and feasible. WHO recommends that antiretrovirals should be started for patients with a CD4 cell count of 350 cells per µL or fewer, and advises against the use of stavudine.[8] Many treatment centres in sub-Saharan Africa are decreasing their threshold for starting antiretroviral therapy to fewer than 200 CD4 cells per µL because of insufficient access to drugs,[9] and stavudine is still widely used because other drugs are too expensive.

Reuters

Patient gets advice about taking antiretrovirals at a clinic in Cape Town's Khayelitsha township

The challenges to treat all patients with HIV infection are enormous. While disease burden is increasing, funds remain the same or are decreasing. Not only do we have to treat more patients, treat them earlier, and provide better drugs, but also we have to treat increasing numbers of patients with resistant viruses[10] (not only because of poor adherence but also because of depleted stocks of antiretrovirals).

There is a growing pessimism among donors about how to deal with the difficulty of HIV treatment in resource-poor settings. There is a move towards control of other diseases with less expensive therapies that are time-restricted and strengthening of health systems instead of provision of antiretrovirals. Funding for HIV treatment should again be put on the international agenda otherwise the efforts of the past will have been in vain.[11]

At the same time, we should improve programme efficiency. The Development of Anti-Retroviral Therapy in Africa (DART) study[12] showed that a greater public health effect would be gained from widening of access to antiretrovirals than by provision of routine laboratory monitoring for patients who are already receiving treatment. Certainly, more research is needed about the role of different laboratory examinations in the scale-up of antiretroviral therapy in resource-limited settings. Testing of targeted viral load[13] instead of CD4 cell count might be the way forward before doctors consider switching patients to more expensive second-line regimens.

We need further research on the integration of antiretroviral services into routine care and we need to expand pre-service HIV education and training instead of the more costly post-service training.[14] As long-term funding for HIV is running flat and access to antiretrovirals is still a huge challenge, HIV research aimed at how to do more with less should be a top priority research issue for the coming years.

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Alcohol: the forgotten drug in HIV/AIDS

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Alcohol has long been recognised as an important contributor to illness and injury, accounting for 4% of the global burden of disease.[1] Yet alcohol remains conspicuously absent from the larger field of research and programming in HIV and substance use. Perhaps because of its very ubiquity, alcohol use remains an easily overlooked backdrop of HIV epidemics worldwide. Patterns of hazardous alcohol consumption prevail in countries with the most severe HIV epidemics, notably eastern and southern Africa (figure: Rehm J, Centre for Addiction and Mental Health, Toronto, ON, Canada; personal communication). In South Africa, for example, where nearly one out of five sexually active adults is HIV positive, the yearly per-capita consumption of alcohol is among the highest in the world.[2] Strikingly, hazardous drinking patterns also dominate in the concentrated epidemics of eastern Europe and Asia, where alcohol use by injecting drug users and other marginalised groups might be an additional barrier to effective efforts to prevent HIV infection.

Many studies in southern and eastern Africa have shown that alcohol use is associated with prevalent and incident HIV infection as well as with the behaviours that lead to infection, including unprotected sex, multiple partnering, and commercial sex.[3] Drinking venues themselves are, not surprisingly, associated with risk of HIV infection.[4,5] The pharmacological properties of alcohol help to explain a portion of the widely observed association between alcohol use and sexual-risk behaviour.[6] A nexus of psychological and social influences also seems to be at play.[7,8] A substantial body of research implicating alcohol consumption in sexual-risk behaviour provides a compelling call to action.

Lessons learned from the small amount of intervention research on alcohol-related HIV-infection risk closely mirrors many of the key messages by Steffanie Strathdee and colleagues in *The Lancet* today.[9] We echo the importance of intervening on the structural and environmental influences that shape risk practices and vulnerability to HIV infection. Because alcohol is a legal