are evaluated, or should it be the more stringent standard of "intolerability" as proposed by the high court? Using a balance sheet standard, clinical judgment may be given greater scope, but with the intolerability standard there is a *prima facie* presumption that life prolonging treatment should be continued if there is some benefit, unless doing so is intolerable for the patient. Here clinical judgment carries less sway.

The appeal court's approach to this thorny issue was singularly brief. It held that it is not possible to attempt to define what is in the best interests of a patient by a single test, and therefore the decision to provide or withhold artificial nutrition and hydration must depend on the particular circumstances of each case. In clinical practice, this can be a poignant and ethically challenging decision, particularly in the sentient but incompetent patient who might be capable of being kept alive indefinitely by artificial nutrition and hydration. The reluctance of the court of appeal to engage in this debate was justified as not being appropriate on the grounds that what was said in the lower court was hypothetical. However, when a patient is close to death, both courts concurred that the purpose of care was to ease the patient's death rather than prolong his or her life and that in this situation intolerability is not necessarily the standard of the patient's best interests.

An advance directive that is valid and relevant to the circumstances refusing continuation of artificial nutrition and hydration in the incompetent patient should be respected on the grounds of autonomy and self determination. However, what of the opposite situation requiring life prolonging treatment? In the original high court judge's analysis such an advance directive should be respected. However, the court of appeal thought this would be incompatible with the provisions of the (not yet in force) Mental Capacity Act 2005. Section 26 of the act requires compliance with a

valid advance directive to refuse treatment. With regard to an advance directive made otherwise section 4 does no more than require this to be taken into consideration when determining the best interests of the patient. However, the legal implications of this point have yet to be tested in the courts.

Meanwhile, doctors should understand and familiarise themselves with current GMC guidance. Clinicians at the sharp end of practice must continue to do as they have always done—approach end of life decision making with empathy, compassion, and reasoned clinical judgment and try to reach a consensus on best interests with the patient, relatives, and wider healthcare team. The high court ruling raised several key issues regarding end of life decisions and the "dilemma at the bedside,"⁵ which were not addressed by the court of appeal. Given time these will surface again, perhaps in the form of a human rights challenge, since many still fear that doctors may make negative stereotypical assumptions about their quality of life at the stage of incompetence. Doctors need to recognise the limitations of their clinical judgment in this context and seek legal advice when there is disagreement about the patient's best interests.

Ash Samanta *consultant rheumatologist*

(ash.samanta@uhl-tr.nhs.uk)

Leicester Royal Infirmary, Leicester LE1 5WW

Jo Samanta *lecturer in law*

De Montfort University, Leicester LE1 9BH

Competing interests: None declared.

- 1 R (the application of Oliver Leslie Burke) v General Medical Council (defendant) and Ors [2005] EWCA Civ 1003.
- 2 R (Burke) v General Medical Council & Disability Rights Commission (interested party) & The Official Solicitor (Intervener) [2004] EWHC 1879.
- 3 General Medical Council. *Withholding and withdrawing life-prolonging treatments: good practice in decision-making*. London: GMC, 2002.
- 4 Re A (Male Sterilisation) [2001] FLR 549.
- 5 Samanta A. Death, dying and the doctor: a dilemma at the bedside. *Contemporary Issues in Law* (in press).

Preventing HIV infection

Needs urgent attention now that effective treatment is widely available

In 2002, the prevailing view was that preventive strategies, rather than the provision of highly active antiretroviral therapy (HAART), were the only feasible way to control the spread of HIV infection.¹ Antiretroviral treatment is now cheaper, thanks to initiatives from the pharmaceutical industry and generic manufacture, and its wider availability encourages more people to seek HIV testing. In line with the "3 by 5" strategy, the World Health Organization aims to provide HAART for three million people by the end of 2005 while continuing to promote prevention. Provision of treatment may be hindered by availability or infrastructural capacity. To make a sustainable impact on the global epidemic of HIV infection, investment in prevention research, including biomedical prophylaxis, remains paramount. Various government campaigns aimed at increasing knowledge and modifying high risk behaviour have

been temporally associated with reduced incidence and prevalence of HIV infection in a few countries, notably Thailand and Uganda.² It remains unclear, however, whether these events are causally related. Phase III studies of potential vaccines against HIV have proved unsuccessful, but there is still hope for other preventive measures. For example, considerable research activity continues to investigate microbicides, with several compounds in development showing promise.³ The necessary phase III trials will not, however, yield results in the near future.

Male circumcision has also been studied widely as a possible preventive measure. Observational studies have suggested that circumcision reduces the risk of acquiring and transmitting HIV infection, although previous meta-analyses did not confirm this.⁴ A recent prospective randomised trial of early circumcision compared with delayed circumcision among

more than 3000 uncircumcised young men was stopped prematurely because of the considerable benefit of early circumcision. Circumcision was offered to men in the intervention group immediately after randomisation and would be offered to those in the control group at the end of follow up. The trial was stopped at the interim analysis after a mean of 18.1 months. Twenty HIV infections occurred in the intervention group and 49 in the control group, corresponding to a rate ratio of 0.40 (95% confidence interval 0.24 to 0.68; $P < 0.001$). When controlling for behavioural factors, including sexual behaviour, condom use, and health seeking behaviour, this ratio corresponded to a protective effect of 61% (34% to 77%).⁵ These data are encouraging but should not elicit a false sense of security and neglect of further preventive measures.

The possibility of chemoprophylaxis before exposure to HIV has caused both interest and marked controversy. Research on monkeys has shown that the antiretroviral drug tenofovir, given up to 48 hours before and after intravenous exposure to HIV, prevents infection.⁶ More recent data show that oral tenofovir reduces, but does not obviate, the risk from subsequent mucosal exposure to the virus.⁷ Researchers gave tenofovir to 12 macaques daily, weekly, or not at all, followed by multiple rectal challenges with simian immunodeficiency virus (SIV). Although tenofovir seemed to protect the macaques initially, eventually all the animals became infected with repeated exposure to the virus.

Randomised controlled trials investigating the use of pre-exposure tenofovir in the prevention of HIV acquisition have recently begun in several countries in both less developed and resource rich settings. Many of these trials have proved extremely contentious,⁸ despite sponsorship or funding from the US National Institute of Allergy and Infectious Diseases, the University of New South Wales, the US Centers for Disease Control and Prevention, and the Bill and Melinda Gates Foundation, rather than the drug company that manufactures tenofovir.

In these ongoing double blinded trials, HIV negative participants were randomised to receive placebo or tenofovir. They were counselled about safer sex and methods of accessing care should they become infected with HIV. Activists have opposed the trials,

citing inadequacies in the overall care of participants, the delivery of proved methods for HIV prevention, the provision of antiretroviral therapy to participants who became infected with HIV during the trial, and the mechanisms for community engagement. These difficulties have led to the closure of the pre-exposure studies in several countries.⁹

Preventing the transmission of HIV infection from mother to child remains a primary goal in the developing world, to emulate successes in Western countries where this risk is kept low through judicious use of HAART and caesarean section. Simply giving a single dose of the non-nucleoside reverse transcriptase inhibitor nevirapine has proved suboptimal in Africa, reducing sensitivity to the drug in a high proportion of mothers as well as offspring and compromising the future effectiveness of this treatment.¹⁰ However, short term combination therapy that includes nevirapine reduces the risk of such drug resistance.¹¹ Given that HIV can be transmitted through breast feeding, strategies such as exclusive breast feeding, which is thought to reduce the risk of diarrhoea and infection in infants, treating mothers with HAART, or chemoprophylaxis for the baby may all reduce transmission rates.¹¹⁻¹³

Rachael Jones *specialist registrar*

(rachaeljones30@hotmail.com)

Brian Gazzard *professor*

Department of HIV and GU Medicine, Chelsea and Westminster Hospital, London SW10 9NH

Yasmin Halima *senior consultant*

International AIDS Society (IAS), Ch. de l'Avanchet 33, CH-1216 Cointrin, Geneva, Switzerland

Competing interests: RJ has received an educational bursary from Gilead, manufacturer of tenofovir, in the last year. BG has received consultancy fees from Gilead in the past five years.

- Creese A, Floyd K, Alban A, Guinness L. Cost effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence. *Lancet* 2002;359:1635-42.
- Kamali A, Quigley M, Nakiyingi J, Kinsman J, Kengeya-Kayondo J, Gopal R, et al. Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. *Lancet* 2003;361:645-52.
- Jiang S, Liu S, Lu H, Neurath AR. Synergistic and complementary effects of the anti-HIV-1 microbicides CAP and UC781 in combination. IAS Conference on HIV Pathogenesis and treatment, Rio de Janeiro, 2005:abstract MoPp0103.
- Halperin DT, Bailey RC. Male circumcision and HIV infection: 10 years and counting. *Lancet* 1999;354:1813-5.
- Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. *PLoS Med* 2005;2(11):e298.
- Tsai CC, Folis KE, Sabo A, Beck TW, Grant RF, Bischofberger N, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonyl-methoxypropyl)adenine. *Science* 1995;270:1197-9.
- Subbarao S. Chemoprophylaxis with oral tenofovir disoproxil fumarate delays but does not prevent infection in rhesus macaques given repeated rectal challenges of SHIV. Twelfth Conference on Retroviruses and Opportunistic Infections, Boston, 2005:abstract 136LB.
- Cohen J. AIDS research. Cambodian leader throws novel prevention trial into limbo. *Science* 2004;305:1092.
- Ahmed K. Trial of antiretroviral for HIV prevention on hold. *Lancet Infect Dis* 2004; 4:597.
- Jackson JB, Becker-Pergola G, Guay LA, Musoke P, Mucana M, Fowler MG, et al. Identification of the K103N resistance mutation in Ugandan women receiving nevirapine to prevent HIV-1 vertical transmission. *AIDS* 2000;14:111-5.
- McIntyre JA, Martinson N, Gray GE, Hopley M, Kimira T, Robinson P, et al. Addition of short course Combivir to single dose Viramune for the prevention of mother to child transmission of HIV-1 can significantly decrease the subsequent development of maternal and paediatric NNRTI-resistant virus. 3rd IAS Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, 2005:abstract TuFoO2O4.
- Iliff PJ, Piwoz EG, Tavengwa NV, Zunguza CD, Marinda ET, Nathoo KJ, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV transmission and increases HIV-free survival. *AIDS* 2005;19:699-708.
- European Collaborative Study. HIV-infected pregnant women and vertical transmission in Europe since 1986. *AIDS* 2001;15:761-70.