EDITORIALS

Editorials are usually commissioned. We are, however, happy to consider and peer review unsolicited editorials
See http://resources.bmj.com/bmj/authors/types-of-article/editorials for more details

Detection of bowel cancer in kidney transplant recipients

Can be achieved safely with colonoscopy screening

Paul A Blaker research registrar, Department of Gastroenterology
David Goldsmith consultant nephrologist, Department of Nephrology, Guy's and St Thomas' Hospitals, London SE1 9RT, UK
david.goldsmith@gstt.nhs.uk

Kidney transplantation is the only cure for progressive kidney failure that requires renal replacement by dialysis. This intervention is successful but limited by increased mortality associated with infection, cardiovascular disease, and cancer. One important cancer related cause of death in this population is colorectal cancer. In a linked research paper, Collins and colleagues study the prevalence of this cancer in kidney transplant recipients aged over 50 years and the diagnostic accuracy of colonoscopy screening in this population.[1]

Although deaths from colorectal cancer are starting to fall in the general population,[2] kidney transplant recipients have a twofold increased risk of de novo colorectal cancer.[3-5] These patients are often younger at diagnosis, and their five year survival rate was also significantly lower than for other patients with colorectal cancer in an observational study that used the National Cancer Institute Survival, Epidemiology and End Result (SEER) database.[6] This worse prognosis is probably related to increased tumour aggressiveness, reduced immunological response, or both.

Clinical practice guidelines for the care of kidney transplant recipients already suggest screening for colorectal cancer from the age of 50 years using faecal haemoglobin testing,[7] which seems to be cost effective.[8] Such screening is not yet uniformly undertaken, however. Moreover, the true prevalence of advanced cancer (adenoma ≥10 cm, villous features, high grade dysplasia, or colorectal cancer), and the ability of faecal haemoglobin testing to detect these lesions, was unknown, until now, for the renal transplant population. There were also no published data on the safety of colonoscopy in renal transplant recipients.

Collins and colleagues' study determined the prevalence and characteristics of advanced colorectal neoplasia in kidney transplant recipients using faecal immunochemical testing for haemoglobin and colonoscopy, and it also evaluated the diagnostic accuracy of these two tests.[1] It therefore investigated the two main problems in detecting and treating advanced colorectal neoplasia in this specific population.

JAMES KING-HOLMES/SPL

Diagnosis by faecal immunochemical testing and colonoscopy was compared

The investigators report a high prevalence of advanced colorectal neoplasia (13%) in their population of 229 patients, with an overall detection of colorectal cancer of 2%. This is higher than the prevalence of advanced neoplasia and colorectal cancer reported in meta-analyses of general population screening studies (5% and 0.78%, respectively).[9]

In line with current guideline based practice in Australia, Collins and colleagues used a faecal immunochemical test to screen for colorectal neoplasia. Faecal immunochemical testing is considered more sensitive and specific than the guaiac faecal occult blood tests that are used in the United Kingdom bowel cancer screening programme.[10] Despite this, the sensitivity of the assay was poor for advanced colorectal neoplasia, although the specificity was reasonable (31% and 90.5%, respectively). This is comparable to other studies in the general population, which have reported an overall sensitivity of 81.8-100% and 27-56.8% for detecting colorectal cancer and advanced adenomas, respectively, and a specificity of 87.5-96.9% and 91.4-97.3%, respectively.[11]

The sensitivity of a single guaiac faecal occult blood test for detecting colorectal cancer is low (12.9-50%), although when it is used repeatedly—for example, in a biennial screening programme—sensitivity can be 51.1-72.2%, with a positive predictive value of 8.0-17%.[12] Future studies in this population should therefore determine the interval of FIT testing that produces optimum sensitivity.

The current study shows that colonoscopy is safe to use as a surveillance tool in kidney transplant recipients. However, colonoscopy is not 100% sensitive, even when the caecum can be visualised—25-50% of adenomas and advanced adenomas are missed, as are 6-12% of larger adenomas (>1 cm) and 4% of cancers.[13] If colonoscopy is used as a screening tool, it must be performed by expert endoscopists who are continuously audited. Future use of chromo-endoscopy and narrow band imaging may increase the adenoma detection rate, particularly with respect to flat or small lesions.

Collins and colleagues enrolled patients aged 50 years and over, which reflects current screening recommendations for the general population in Australia, Canada, and the United States. A study using information from the Australian and New Zealand Dialysis and Transplant Registry database assessed the site specific cancer risk across different patient groups for 15 183 kidney transplant recipients. For age groups under 35 years, 35-44, 45-54, and over 55 years the standardised rate ratio for colorectal cancer compared with the general population was 13.51, 6.88, 3.66, and 2.66 for women, and 6.73, 1.27, and 1.12 for men.[14] Younger patients (<55 years) had the greatest risk of developing colorectal cancer. A further study showed that patients under 50 years with solid organ transplants had a significantly higher risk of colorectal cancer compared with the general population (incidence ratio 3).[15] Such evidence suggests that kidney transplant recipients may need to be screened for colorectal cancer (well) before the age of 50 and that earlier screening should now be trialled.

Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

References are in the version on bmj.com.

Cite this as: *BMJ* 2012;345:e5081

RESEARCH, p 17

bmj.com For all the latest on cardiology visit the *BMJ* cardiology portal at http://bit.ly/MnSoOq

Psychological distress and death from cardiovascular disease

May be related in a dose-response manner, but it is not clear how to intervene

Glyn Lewis professor, University of Bristol, Bristol BS8 2BN, UK glyn.lewis@bristol.ac.uk

The association between psychiatric disorders and cardiovascular disease is often reported in observational studies, but the question of reverse causation has always loomed large. In a linked research study, Russ and colleagues investigated the association between psychological distress and death from cardiovascular disease (recorded on death certificates) by examining data on more than 60 000 people from 10 large cohort studies based on the Health Surveys for England.[1] The authors excluded early deaths (in the first five years of follow-up) and therefore the likelihood of reverse causation. Although the possibility of confounding can never be completely excluded, after adjusting for several "lifestyle" factors and cardiovascular disease risk factors, the authors still found a dose-response association between psychological distress and death from cardiovascular disease. These findings add to evidence that suggests a causal association between psychological distress and cardiovascular disease.

In the English health surveys used by Russ and colleagues, psychological distress was measured using the General Health Questionnaire (GHQ).[2] This assessment of mental health status is widely used and shows good agreement with more detailed assessments of depression and anxiety, conditions that are best represented along a continuum of severity in population studies.[3] No obvious point separates people who report symptoms of depression or anxiety that meet diagnostic criteria from those who report similar symptoms below the diagnostic threshold. The current study found that an increased risk of cardiovascular disease exists along the whole of this continuum in a dose-response manner. Forty per cent of the sample scored at least 1 on the GHQ, and an association with subsequent death from cardiovascular disease was seen even at these low scores. The prevalence of depression and anxiety disorders is about 7.5% in the United Kingdom.[4] It is now clear that an association between psychological distress and cardiovascular disease exists well below the threshold that would lead to a diagnosis of depression or anxiety or require specific treatment.

Several plausible mechanisms might explain how psychological stress can lead to cardiovascular events.[5 6] The stress response involves the hypothalamus-pituitary-adrenal axis and the autonomic system; changes in inflammatory cytokines might also be implicated. What is the difference, if any, between stress and psychological distress? Stress is usually defined as the response of an organism to external stressors. One idea that has gained popularity is that the physiological and psychological responses to psychological stressors are designed to protect the organism but that the body's response can also have harmful effects on health.[7] It seems reasonable to hypothesise that not "coping" with psychological stressors will lead to symptoms of depression and anxiety; in other words, psychological distress and psychological stress are the same thing. Using the GHQ or other similar measures to assess sub-threshold symptoms at a given time point may be one way of assessing stress levels. It is also important to distinguish between acute and more chronic forms of stress.[5 6] Watching the English football team lose a penalty shootout, which has also been associated with cardiovascular events,[8] may be acutely stressful. The stress measured by the GHQ is more likely to be chronic.

People vary greatly in their response to stressors… avoiding stressors might also lead to more anxiety in the long run

It is difficult to make the leap from the current observational evidence to suggesting that reducing stressors in the environment or changing the psychological interpretation of stressors will help to prevent cardiovascular disease. But, if psychological stress and distress are causes of cardiovascular disease, what implications does this have for prevention and treatment? For those people who meet diagnostic criteria for depression and anxiety, several effective psychological and drug treatments are available. However, what should be done about the much larger numbers of people who report symptoms on the depression-anxiety continuum but do not meet diagnostic criteria?

Obvious sources of stress such as workplace stress could be modified.[6] It is also worth considering how societal stresses related to inequalities and socioeconomic status might contribute to the incidence of cardiovascular disease.[9] However, an attempt to produce a stress-free existence seems utopian and ignores the idea of "good stress."[7] People vary greatly in their response to stressors, and some people even seek out stressors to provide a challenge and a sense of achievement. Avoiding stressors might also lead to more anxiety in the long run.[10]

A more useful approach could be to change the psychological interpretation of stressors, because this might reduce their biological impact. Cognitive behavioural therapy is, in part, designed to help people change the way they interpret stressors and thereby reduce the impact of stress.[11] Individual and group cognitive behavioural therapy has been shown to be an effective treatment for depression and anxiety, but not, sadly, for preserving the health of the English football team's supporters. Even if we could improve our understanding and use of cognitive theories in the population to increase resilience to stressors, there is currently no evidence that these methods can be disseminated to the population at large to help people reduce perceived stress.

Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimäki M, Batty GD. Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *BMJ* 2012;345:e4933.
2 Goldberg DP, Williams P. The user's guide to the General Health Questionnaire. NFER-Nelson, 1988.
3 Lewis G, Araya R. Classification, disability and the public health agenda. *Br Med Bull* 2001;57:3-16.
4 NHS Information Centre. Adult psychiatric morbidity in England 2007: results of a household survey. 2009. www.ic.nhs.uk/pubs/psychiatricmorbidity07.
5 Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet* 2007;370:1089-100.
6 Steptoe A, Kivimaki M. Stress and cardiovascular disease. *Nat Rev Cardiol* 2012;9:360-70.
7 McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998;338:171-9.
8 Carroll D, Ebrahim S, Tilling K, Macleod J, Smith GD. Admissions for myocardial infarction and World Cup football: database survey. *BMJ* 2002;325:1439-42.
9 Brunner E. Stress and the biology of inequality. *BMJ* 1997;314:1472-6.
10 Marks IM. Living with fear. understanding and coping with anxiety. McGraw-Hill, 1980.
11 Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive therapy of depression. Wiley, 1979.

Cite this as: *BMJ* 2012;345:e5177

RESEARCH, p 14

bmj.com
For all the latest on oncology visit the *BMJ* oncology portal at http://bit.ly/MnSoOq

Biological age is best determined by some form of comprehensive geriatric assessment

Treating cancer in older people

Assessing biological age could help to avoid undertreatment

Alistair Ring senior lecturer in oncology, Brighton and Sussex Medical School, Sussex Cancer Centre, Brighton BN2 5BE, UK alistair.ring@bsuh.nhs.uk

In March 2012 Macmillan Cancer Support, one of the United Kingdom's biggest cancer charities, launched their Age Old Excuse campaign. This campaign called for older people with cancer to be offered treatment on the basis of their physical fitness rather than their age.[1] Survival rates for older patients with cancer in the UK lag behind those in other comparable countries.[2]

In the UK, 155 000 people aged 70 years or more are diagnosed with cancer every year. This number represents 50% of all cancer diagnoses,[3] and it is likely to rise as the population ages. The challenge of treating older adults diagnosed with cancer is not unique to the UK, and the European Organisation for the Research and Treatment of Cancer has convened an "elderly task force" to look at key questions.[4]

Poor cancer survival rates in older adults may be partly explained by undertreatment.[1 5] Some older patients may decline or choose to receive less aggressive treatment. Clinical reasons for offering less intensive treatment include frailty and comorbidity that would render patients less likely to tolerate treatments such as surgery, chemotherapy, and radiotherapy. Chronological age alone, however, is a poor proxy for treatment tolerance; many older patients have relatively few health problems and may tolerate cancer treatment as well as their younger counterparts.[6] Nonetheless, age remains a key determinant in decision making.[7] Macmillan Cancer Support's campaign called for older patients to be offered treatment on the basis of their fitness and not their chronological age, and this is welcome as a stimulus for action. However, developing robust measures of so called biological age and incorporating them into clinical practice presents several challenges.

Biological age is probably best determined by some form of comprehensive geriatric assessment, which might include measurements of comorbidities, functional status, cognition, nutrition, psychological state, and social support. Although several scales are available to measure each of these domains, there is little consensus on which to use for this patient group, or even which domains to include. This makes interpreting and comparing different research outputs difficult, and consensus on the domains to include in such an assessment is needed before real progress can be made.

However, cancer specific tools may be needed because it is not certain that assessments of global health status developed in the inpatient or community geriatric population will accurately predict relevant outcomes in older patients with cancer. Formal assessments might help to identify those older patients whose life expectancy is limited by their pre-existing frailty and who will die from other causes before the benefits of anticancer treatment are realised. Yet currently few data validate the use of a comprehensive geriatric assessment in this way. Robust validation would require prospective studies that may take many years to complete. In addition, data describing the usefulness of such assessments as a predictor of treatment toxicity are limited. It would be premature, therefore, to make treatment recommendations (in particular withholding treatment) on the basis of such tools at this time. Some clinicians might claim that they already take many relevant factors into account, informally and subjectively, and that formalised tools may be unnecessary.

Even if a standard assessment could be agreed on and validated against clinically relevant outcomes, delivery remains a challenge. A comprehensive assessment may take as long as an hour to complete and would involve input from several members of the geriatric multidisciplinary team. Although it may be possible to use screening tests to identify those in need of a full assessment, the process is inevitably time consuming. Furthermore, one important reason for conducting an assessment is to identify reversible health problems that, if dealt with, might render the patient fit enough for treatment. If such assessments are to be conducted, systems should be in place for accessible and timely onward referral to relevant specialist or multidisciplinary services, with a view to delivering anticancer treatment in an acceptable time frame.

Assessment tools are not a panacea; they will not solve the problems of delayed diagnosis, limited evidence base for treatment, and (in some areas) prevailing attitudes about the value of treating cancer in older patients. Nonetheless, the survival and experience of older adults diagnosed with cancer would probably be improved by developing more formal assessments of fitness and delivering optimum cancer care to older patients who can tolerate it. It is important to overcome the challenges even though this will require investment in the development of assessment tools, training, and service infrastructure.

Competing interests: AR is lead for one of the Macmillan pilot sites for older people's cancer research and a UK representative on the European (EORTC) task force for cancer in the elderly.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Macmillan Cancer Support. The age old excuse: the under treatment of older cancer patients. 2012. www.macmillan.org.uk/Documents/GetInvolved/Campaigns/AgeOldExcuse/AgeOldExcuseReport-MacmillanCancerSupport.pdf.
2 Moller H, Flatt G, Moran A. High cancer mortality rates in the elderly in the UK. *Cancer Epidemiol* 2011;35:407-12.
3 Cancer Research UK. Cancer incidence by age—UK statistics. 2012. http://info.cancerresearchuk.org/cancerstats/incidence/age/.
4 Pallis AG, Ring A, Fortpied C, Penninckx B, Van Nes MC, Wedding U, et al. EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors. *Ann Oncol* 2011;22:1922-6.
5 Department of Health. Reducing cancer inequality: evidence, progress and making it happen: a report by the National Cancer Equality Initiative, 2010. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114353.
6 Quoix E, Zalcman G, Oster JP, Westeel V, Pichon E, Lavolé A, et al. Weekly paclitaxel combined with monthly carboplatin versus single-agent therapy in patients age 70 to 89: IFCT-0501 randomized phase III study in advanced non-small cell lung cancer. *Lancet* 2011;378:1079-88.
7 Department of Health. The impact of patient age on clinical decision-making in oncology. 2012. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_132796.

Cite this as: *BMJ* 2012;345:e4954

bmj.com

- News: UK patients' reports of adverse reactions are more detailed than doctors' (*BMJ* 2011;342:d3160)
- Views and reviews: Death of the silent witness: patients' reporting of adverse drug reactions (*BMJ* 2011;342:d4042)

Drug safety: reporting systems for the general public

WHO's latest guidance is relevant to developed and developing countries

June Munro Raine director of vigilance and risk management of medicines, Medicines and Healthcare Products Regulatory Agency, London SW1W 9SZ, UK
june.raine@mhra.gsi.gov.uk

Harms from drugs are an important cause of morbidity, mortality, and extra costs to healthcare.[1] Such costs are high in developed countries—the average treatment costs of a single adverse drug reaction in Germany were recently estimated to be €2250 (£1766; $2762).[2] The costs to healthcare delivery in developing countries could be even greater, because real harm to even a few patients can destroy the credibility and success of an important public health programme. Public concern about adverse effects of drugs can spread rapidly and is difficult to refute in the absence of good data.[3 4] The latest guidance on monitoring the safety of drugs from the World Health Organization focuses on planning and implementing adverse drug reaction systems for the general public and will probably make an important contribution to pharmacovigilance strategies.[5]

Spontaneous reporting systems remain a core element of pharmacovigilance—the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problem. But is the WHO report relevant to countries with an existing consumer reporting scheme (Australia, Canada, Denmark, Netherlands, Sweden, United Kingdom, and United States) or only to those who are yet to establish one? The answer, it seems, is yes.

The value of consumer reporting as an integral part of pharmacovigilance has not always been recognised. It took some powerful examples of important observations by lay users to change perceptions of users' potential to contribute valuable information on drug safety. These include lipodystrophy associated with certain anti-HIV drugs and debilitating effects associated with selective serotonin reuptake inhibitors, particularly on withdrawal.[6 7]

A review conducted on the 40th anniversary of the UK's Yellow Card scheme in 2004 concluded that it should be opened up to consumer reporting, despite the worry that this might make it more difficult to detect "real" signals of drug safety concerns because of the additional "noise."[8] Subsequently, an analysis of 26 129 reports made by patients and health professionals, of which 20% were made by patients, showed that more signals were detected when reports of suspected adverse reactions from both consumers and health professionals were collated. Moreover, patients' descriptions of suspected adverse reactions were more detailed than those of health professionals and were more likely to explain the effect of the reaction on the patient's life.[9]

PAUL RAPSON/SPL

A review of the UK's Yellow Card scheme concluded that it should be opened up to consumer reporting, despite the worry that this might make it more difficult to detect "real" signals of drug safety concerns

For countries that are yet to introduce consumer reporting of adverse drug reactions, the new guidance issued by WHO provides comprehensive advice on which questions need to be considered and which stakeholder organisations should be involved. As a step by step guide to implementing a well organised and effective consumer reporting system, it is applicable to developing countries and developed countries that lack the systems for consumers to report drug reactions. In this regard, its publication is particularly opportune for European Union countries, which are now required to accept consumer reports by new EU-wide legislation that came into force in July 2012.[10 11]

The WHO guidance is also relevant to countries whose existing systems need to be improved or strengthened. In advising that there should be no restrictions to the drug related harms that consumers can report it is in tune with the extended scope of an adverse drug reaction as defined in the new EU legislation. This definition now includes harms associated with medication error, off-label use, unlicensed use, and misuse. As the WHO guidance clearly states, all reports are welcome and useful.

In addition, at this time of increasing concern about counterfeit drugs entering the supply chain, reports from patients can help identify such drugs. For example, a patient on olanzapine, who had taken to polishing his tablets, reported that the colour in the coating was rubbing off. When the drug's ineffectiveness was also deduced this led directly to identification and action on a major counterfeit operation.

Importantly, the WHO guideline recognises the role of the medicines regulator to evaluate new drug safety signals and take prompt and proportionate regulatory action to minimise risk. However, the guideline envisages the regulatory function as quite distinct from safety monitoring. In developed countries, pharmacovigilance is generally closely aligned with or integrated in regulatory agencies that are responsible for monitoring the benefit-risk balance throughout a drug's lifetime in clinical use. In countries with no legal base for pharmacovigilance, public health protection is limited by the inability of regulatory authorities to enforce the responsibilities of drug companies for post-marketing safety activities.[12] In particular, the companies' responsibilities for surveillance of the safety of donated drugs must be clarified.

Notwithstanding these qualifiers, the WHO guidance has general relevance and goes a long way to setting standards for consumer reporting of adverse reactions so that its potential to contribute useful information on drug safety can be maximised. The report's timing in terms of influencing new and evolving pharmcovigilance systems could not be better. Even well established consumer reporting schemes—such as the UK's Yellow Card—evolve over time, and with international data exchange a suspected adverse reaction reported via a local system could help to prevent harms from a drug worldwide.

Competing interests: The author has completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; JMR is a member of the World Health Organization advisory committee on safety of medicinal products.

Provenance and peer review: Commissioned; not externally peer reviewed.

References are in the version on bmj.com.

Cite this as: *BMJ* 2012;345:e4916

Rounds themselves are not a solution for poor quality care and cannot compensate for inadequate leadership

Nurse leadership and patient safety

Rounding can enhance but not ensure patient safety; better to focus on appropriate training

Çakıl Agnew research fellow c.sarac@abdn.ac.uk
Rhona Flin professor of applied psychology , Industrial Psychology Research Centre, School of Psychology, University of Aberdeen, Aberdeen AB24 3UB, UK
Jane Reid visiting professor, Bournemouth University, Dorset, UK

The UK government recently called for better nurse leadership and ward management[1]—for example, by calling for nurses to undertake hourly rounds—after increasing concern about the quality of patient care in the NHS. In response, the Royal College of Nursing commented that ward sisters are experienced nurses who can provide expert leadership to the team, and that they need to be able to call the shots and supervise and develop the wider workforce.[2] The college's response signals recognition that ensuring safe care is less about pronouncements from Whitehall and more to do with local ownership of local problems, underpinned by committed and effective leadership at all levels of the organisation.

The prime minister's call to improve nursing quality through "intentional rounding"—a formal process of patient checks conducted by responsible nursing staff every one to two hours—implies that nurses would improve care merely by focusing on patients rather than on tasks. Ironically, "back rounds"—a series of nurse led actions focused on specific care needs—were cast into the wilderness by leaders in the mid-1980s, as diminishing "individualised care." Rounds provide a means of checking that patients are comfortable and that their needs (physical and psychological) are being met, while providing an opportunity for patients and their families to identify a "visible figure of nursing authority." Intentional rounding that focuses on patients' needs has been shown to improve pain management and to reduce falls, dehydration, and the prevalence of pressure sores. Intentional rounding is promoted by the King's Fund, a UK health policy think tank, as a valuable example of how ward leaders can monitor patient care and comfort, but rounds themselves are not a solution for poor quality care and cannot compensate for inadequate staffing or poor leadership.

Solutions for quality improvement are inevitably multifarious, and to assure safe, effective, and high quality experiences for patients, their implementation depends on excellent leadership. The need to instil public trust and confidence in the leadership skills of ward nurses is greater than ever given current financial challenges in the NHS and the impending report of the Francis Inquiry. Charge nurses and ward sisters must meet a variety of expectations in their roles, which include both delivery of quality clinical care and managerial duties, and this requires a high level of leadership competence. The extent to which the Department of Health, trust boards, and the public can expect nurse leaders to keep patients safe without properly preparing them to meet these demands should not be a rhetorical question, but one that prompts action for evidence gathering.

JOHN COLE/SPL

Rounding involves regular formal checks on patients' needs

In high risk industries, leadership is recognised as an essential aspect of safety management,[3] and this has resulted in the delivery of specific safety leadership programmes for all levels of managers. Interventions that target safety related monitoring, and those that reward behaviours of supervisors and motivate employees to make the workplace safe, have been shown to increase the safety behaviours of workers and reduce occupational injuries.[3]

Leadership at the level of the hospital ward is no different from other domains where safety is crucial. It is essentially about "influencing others to understand and agree about what needs to be done and how to do it, and the process of facilitating individual and collective efforts to accomplish shared objectives."[4] Although evidence is available on the impact of nurses' leadership styles on organisational outcomes,[5] very little research has investigated the effect of their leadership behaviours on safety related outcomes.[6] Some studies of ward leadership are beginning to include patient safety outcomes, such as adverse events, patient falls, drug errors, and infection rates, but the results do not show a consistent pattern. For example, relationship oriented leadership behaviours of nurses (such as being approachable and giving feedback) were related to reduced adverse events in 164 nursing homes in the United States.[7] Similarly, indirect effects of relational leadership (setting an example as a leader) of nurse managers in 46 US patient care units reduced patient falls and drug errors.[8] In contrast, the level of support given to nurse managers was not related to the frequency of patient adverse events in 21 surgical and medical wards.[9]

The specific leadership behaviours most effective in determining a safer ward environment need to be established before initiating more leadership policies for nursing aimed at maximising patient safety. Despite the generic guidance within the NHS Leadership Framework, little empirical evidence specifies which of the leadership skills designed to increased patient safety are the most effective, either for nurses or for other clinicians.

Leadership practices are regarded as a key factor that influences nurses' motivation and performance.[10] Without training that focuses on safety how can we ensure that frontline NHS leaders do not unwittingly, and in response to economic imperatives, "drift" the system close to the boundaries of safety?[11] Nurses' leadership development requires more than political rhetoric or temporary interest to safeguard the quality of care delivered to patients in the NHS. It needs evidence based leadership training programmes designed for nurse leaders. Investing in the leadership potential of nurses should be a priority.[12]

Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

References are in the version on bmj.com.

Cite this as: *BMJ* 2012;345:e4589

bmj.com

- Observations: The myth of an AIDS free world (*BMJ* 2012;345:e5479)
- Feature: The slow and unknown route to a cure for AIDS (*BMJ* 2012;345:e5265)
- Blog: Judit Rius Sanjuan: Do no harm—how a US led free trade agreement threatens the prospects for an AIDS free generation

HIV pre-exposure prophylaxis

A once daily pill reduces risk in some groups but implementation will be challenging

Stephen F Morin professor of medicine and director, center for AIDS prevention studies steve.morin@ucsf.edu
Gavin Yamey lead, evidence to policy initiative, global health group
George W Rutherford professor of epidemiology, preventive medicine, and pediatrics , University of California, San Francisco, CA 94105, USA

On 16 July 2012, the US Food and Drug Administration (FDA) approved a fixed dose combination of tenofovir disoproxil fumarate and emtricitabine (TDF-FTC; Truvada) as a once daily pill for prevention of HIV infection in at risk adults.[1] Approval of this combination for pre-exposure prophylaxis is one of several reasons why some HIV experts believe "the end of AIDS" is in sight.[2] But is such optimism justified?

The excitement about this treatment is understandable given that the HIV epidemic in the United States persists,[1] mainly among men who have sex with men and African-Americans. Condoms are effective at preventing HIV,[3] but their use is inconsistent.[1] Identifying and treating every infected person to achieve viral suppression could reduce transmission (so called treatment as prevention),[4] but such treatment expansion is still a long way off. Therefore, pre-exposure prophylaxis could, in theory, produce population level reductions in HIV transmission.

JEFF CHIU/AP/PA

Pre-exposure prophylaxis was not beneficial in all trials

The efficacy of TDF-FTC for pre-exposure prophylaxis was demonstrated in two large randomised double blind placebo controlled trials, which were the basis for its approval by the FDA. The multinational Pre-exposure Prophylaxis Initiative trial, which looked at 2499 HIV negative men or transgender women who have sex with men who reported high risk behaviour, found a 44% reduction in incidence (95% confidence interval 15% to 63%; P=0.005).[5] A pre-exposure prophylaxis trial in Kenya and Uganda of 4758 HIV serodiscordant heterosexual couples found a 75% reduction in HIV infection (55% to 87%; P<0.001).[6] In both trials, efficacy was strongly correlated with adherence.

The FDA also noted, however, that pre-exposure prophylaxis was not beneficial in all trials. One trial of oral daily TDF-FTC in high risk women was stopped early for futility.[7] In a second trial, also in women, which had five arms (daily tenofovir vaginal gel, daily oral TDF, and daily oral TDF-FTC compared with respective gel and oral placebos), the oral TDF and TDF gel arms were stopped because no protection against HIV was seen.[8] These outcomes may have been related to poor adherence.[1] Pre-exposure prophylaxis works by supplying a therapeutic level of antiretroviral drugs in the bloodstream before exposure to the virus, so it is crucial that adequate levels of drug are present in the system.

The FDA determined that TDF-FTC had an acceptable risk-benefit ratio. No new side effects were identified across the clinical trials. Nonetheless, a recent study with in-depth interviews on health providers' views about implementing this prevention strategy found widespread concern about the use of a potentially toxic drug in otherwise healthy people.[9]

FDA approval included a risk management plan for training prescribers. It also included outreach to educate uninfected people considering prophylaxis about the risk of developing drug resistant variants that could complicate treatment if they became infected while taking prophylaxis. Potential patients need to have a negative HIV-1 antibody test before starting prophylaxis. The FDA recommends monitoring visits every three months to assess physical status, testing for HIV to confirm that the patient has remained uninfected, and checking for drug side effects.

On the basis of data reviewed by the FDA, serodiscordant couples and high risk men who have sex with men would benefit the most from pre-exposure prophylaxis. However, US providers who see large numbers of men who have sex with men do not agree on the most appropriate patients for prophylaxis, and clear practice guidance on screening for risk needs to be developed.[9]

TDF-FTC is expensive, with cost estimates in the US market of more than $1000 (£640; €810) for a one month prescription.[10] Insurance providers may be motivated to cover such treatment because of the high lifetime cost associated with HIV infection. But it is unclear how such costs would be covered in publicly financed programmes. The law is clear that HIV related services can be provided only to people infected with HIV. No parallel programme currently exists for uninfected people.

Public health systems typically see adult patients in drop-in clinics, such as sexually transmitted disease clinics, on a one time basis, and they do not regularly monitor patients over time. Providers do not believe that the current models of care are well suited to prescribing pre-exposure prophylaxis.[9]

Large scale implementation of pre-exposure prophylaxis therefore faces formidable challenges. More research will be needed to assess the comparative value of pre-exposure prophylaxis against treatment as prevention.

There is still no effective vaccine against, and still no cure for, HIV. Pre-exposure prophylaxis adds another potentially valuable tool to our growing list of containment strategies, but by itself it is unlikely to signal the end of AIDS.

Competing interests: SFM declares that the Center for AIDS Prevention Studies has received funds from the Gladstone Institute of Virology and Immunology/UCSF Center for AIDS Research, which has supported trials of pre-exposure prophylaxis; SFM declares that the Center for AIDS Prevention Studies has received funds from the Bill and Melinda Gates Foundation, which has supported trials of pre-exposure prophylaxis; SFM declares that the Center for AIDS Prevention Studies has received funds from the California HIV/AIDS Research Program, which has supported research projects on pre-exposure prophylaxis; SFM declares that the Center for AIDS Prevention Studies has received funding from the US Presidential Emergency Plan for AIDS Relief, a major funder of antiretroviral drugs, through the Centers for Disease Control and Prevention. GY declares that the Evidence to Policy initiative (E2Pi) has received funding from the Bill and Melinda Gates Foundation, which has supported trials of pre-exposure prophylaxis; GY declares that E2Pi has received funding from the Global Fund and UNITAID, two major global funders of antiretroviral drugs. GWR declares that the Institute for Global Health has received funding from the Bill and Melinda Gates Foundation, which has supported trials of pre-exposure prophylaxis; GWR declares that the Institute for Global Health has received funding from the World Health Organization, which develops recommendations for the use of antiretroviral drugs; GWR declares that the Institute for Global Health has received funding from the US Presidential Emergency Plan for AIDS Relief, a major funder of antiretroviral drugs, through the Centers for Disease Control and Prevention.

Provenance and peer review: Commissioned; not externally peer reviewed.

References are in the version on bmj.com.

Cite this as: *BMJ* 2012;345:e5412