PEPSE

Can the promotion of post-exposure prophylaxis following sexual exposure to HIV (PEPSE) cause harm?

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Health policy decisions should be based on sound evidence

Sustained increases among homosexual men of unsafe sexual behaviour, sexually transmitted infections, and HIV have caused much concern.[1] HIV transmission among homosexual men continues despite the use of antiretroviral therapy that lowers infectiousness.[2] The idea that ''treatment optimism'' has led to ''behavioural disinhibition'' has attracted much attention although recent data suggest it is by no means the whole story.[3]

Guidelines for the administration of antiretroviral drugs as post-exposure prophylaxis following non-occupational or sexual exposure (termed nPEP in the United States and PEPSE in the United Kingdom) have been drawn up in both the United Kingdom[4] and the United States.[5] These guidelines offer advice on when to give prophylaxis and to whom. Both guidelines acknowledge that the evidence in support of the recommendations is not watertight. Much of the evidence is inferred from retrospective data on occupational exposure,[6] the use of antiretroviral therapy to reduce mother to child transmission of HIV,[7] and on experimental simian immunodeficiency virus (SIV) and HIV-2 infections in macaques.[8 9] The data suggest that PEPSE can reduce the risk of infection with HIV if administered promptly (less than 72 hours after exposure) and continued for 28 days. A non-randomised study among 202 homosexual men provided with access to PEPSE in Brazil suggested that there were 81% fewer seroconversions among those who took medication but was still not conclusive.[10] Other research suggests most homosexual men who receive PEPSE are more careful for periods of up to two years.[11] Waldo *et al* were unable to demonstrate that the availability of PEP in San Francisco was increasing risk behaviour in homosexual men generally.[12] The most recent health economic evaluation of PEPSE in the United States has concluded that PEP for sexual or injection drug exposure would be cost effective across 96 metropolitan areas.[13] In general, studies suggest that maximum cost effectiveness would be achieved if PEPSE were given following receptive anal intercourse with a partner at high risk of infection or high risk exposures with a partner known to be infected. Even in San Francisco, 217 homosexual men reporting unprotected receptive anal intercourse with a partner of unknown status would need to be treated with PEPSE to prevent one transmission.[13]

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A question that remains unanswered is what is the effect on the highest risk behaviours at a population level, of making PEPSE available on demand. The most desirable outcome (which is presumed by both guidelines) is that promoting PEPSE will cut rates of HIV infection in exposed individuals and reinforce safer sexual behaviour. Another possibility is that the promotion of PEPSE will make no difference to the epidemic with the numbers protected being counterbalanced by additional infections in men whose risk behaviour is increased by awareness of PEPSE but who then fail to obtain it or to respond to it. This outcome is consistent with the theory of risk homoeostasis developed by psychologist Gerald Wilde which posits that where an intervention to reduce risk is introduced, any protective gains tend to be counterbalanced by losses among individuals who increase their risk exposure too much.[14] Should this prove to be the case with PEPSE, as we have suggested previously,[15] then evaluations of the cost effectiveness of PEPSE could reach very different conclusions.

In the central London clinic where two of us work PEPSE was given to 48 patients in 2003 and 119 in 2004. The projected cost of PEPSE drugs alone for 2005 is £180 000. Our HIV clinics are experiencing significant service and cost pressures since the introduction of the PEPSE guidelines and the publicity campaign by the Terence Higgins Trust, aimed at increasing awareness of PEPSE among homosexual men and encouraging them to approach clinics for advice. Since the start of the publicity campaign, relative increases in those obtaining PEPSE in a south west London clinic have been similar to those in north London despite this clinic not being identified in the publicity material.

The most serious question that has to be asked about PEPSE is whether it could cause net harm, protecting only a few individuals at the expense of adverse effects on behaviour and increased HIV transmission in the wider community. Increases in unsafe sexual behaviour among homosexual men have been reported in many countries in the past few years. The coincidence of this phenomenon with improved therapy has attracted much speculation and debate.[1] With this background it seems legitimate to ask whether promoting PEPSE could exacerbate these trends. Clinicians, who rightly focus on helping the individual, may be reluctant to examine this possibility but it must be taken seriously when there is an expanding epidemic. We are concerned that there is pressure to make PEPSE available for homosexual men regardless of cost and without proper consideration of possible negative consequences on service delivery and HIV transmission. Local commissioners of HIV healthcare services in the United Kingdom have not been involved in decisions on the provision of PEPSE. We fear a backlash from unfavourable public opinion if large sums are to be spent without adequate evaluation on a measure of unproved efficacy at the individual level and with the potential to disinhibit safer sexual behaviour generally. Media interest could also lead to increasing numbers of heterosexuals seeking PEPSE, a situation in which PEPSE will rarely be cost effective in the United Kingdom.

Health policy decisions should be based on sound evidence. We conclude, firstly, that the scientific community has a responsibility to consider and attempt to measure the impact of PEPSE on clinical outcomes, behaviour, and attitudes, both at the individual and community level, in order to demonstrate whether it is beneficial or harmful. Secondly, until the evidence is clearer, we would question the wisdom of a national campaign publicising access to free provision of PEPSE. We believe there is a distinct danger that the promotion of PEPSE could reinforce rising trends in risky sexual behaviour

and might add to, rather than lessen, HIV transmission.

ACKNOWLEDGEMENTS

This editorial was written following discussion with many colleagues. In particular we would like to thank the following for suggestions: Paul Benn, Jackie Cassell, Richard Gilson, John Imrie, Kevin Miles, Angela Robinson, Ian Weller, Mark Pakianathan, Helen Pritchitt, and Wendy Majewska.

Sex Transm Infect 2005;**81**:190–191.
doi: 10.1136/sti.2005.014886

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PEPSE

Can the promotion of post-exposure prophylaxis following sexual exposure to HIV (PEPSE) cause harm?: Response

M Fisher

Many countries are utilising such therapies as one method of HIV prevention

Richens *et al* question whether the development of guidelines for the provision of post-exposure prophylaxis following sexual exposure (PEPSE) will cause harm, based on three areas of concern: doubts over efficacy, possible effects on sexual behaviour, and cost.

The efficacy of PEPSE has yet to be determined in a robust fashion. As Richens *et al* observe, data to support the UK[1] (and other) guidelines have been drawn from animal models, vertical transmission studies, retrospective data from healthcare workers exposed to HIV, and prospective (unrandomised) studies in men who have sex with men (MSM),[2] and individuals following sexual assault.[3] In the latter two case-controlled studies HIV seroconversion in PEPSE recipients was 0.6% and 0% compared to 4.2% and 2.7% in controls, supporting its putative efficacy. It is highly unlikely that a prospective randomised study to address the fundamental question of efficacy would be possible (given the numbers involved to achieve sufficient power) or acceptable from an individual or ethical perspective. Whether the absence of such data should result in a failure to offer a potentially beneficial intervention is questionable. Although we live in an era where evidence based medicine is the holy grail, the majority of medical interventions are not supported by high levels of robust evidence from randomised studies. The provision of PEP to healthcare workers following actual or potential exposure to HIV is open to similar criticisms, but the routine adoption of PEP in this setting is not questioned by Richens *et al*, nor indeed by UK or other national policies. This is despite a marked difference in risk of transmission involved in comparing these scenarios. For example, the risk to a healthcare worker following a needlestick injury from a homosexual man of unknown HIV serostatus is 0.045%, whereas the risk following receptive anal intercourse from a known HIV positive "donor" is at worst 3%, and from an undetermined source 0.45%. Is it ethical to withhold a potentially beneficial though not "AI" evidence based intervention in one situation (of higher risk) but provide it freely in the other? To do so would seem to challenge the basic biomedical ethical principles of justice and beneficence.

Richens *et al* quite rightly identify that one of the major concerns regarding the routine provision of PEPSE is the potential for a resulting change in risk behaviour such that individuals will engage in high risk activity in the knowledge that PEPSE is available. However, contrary to these concerns, all available data suggest that this is not the case. In the two studies that have examined behaviour after individuals have taken PEP the opposite appears to occur. In Brazilian MSM, risk behaviour declined over time (in both PEP users and non-users),[2] and in San Francisco 73% reported a decrease in high risk sexual acts.[4] Clearly, there are limitations to these data. Firstly, it remains to be determined whether such changes in sexual behaviour occur in other settings (such as the United Kingdom). Secondly, these studies have only examined changes in behaviour in individuals who have received PEP and not the wider community. Those studies that have attempted to address the possible effects of availability of PEP have suggested that awareness does not result in an increase in risk taking.[5 6] It is well