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Current Opinion in Infectious Diseases was launched in 1988. It is part of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of infectious diseases is divided into 12 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal’s Editors, and the Section Editors for this issue.

Editors

Vincent T. Andriole

Vincent T. Andriole, MD, is Professor Emeritus of Medicine at Yale University School of Medicine and Attending Physician at Yale-New Haven Hospital in New Haven, Connecticut. Andriole received his Bachelor of Science degree from the College of Holy Cross in Worcester, Massachusetts and his medical degree from Yale University School of Medicine. He completed his postgraduate training at North Carolina Memorial Hospital, National Institutes of Allergy and Infectious Diseases/National Institutes of Health, and Yale University School of Medicine. Dr Andriole is a member of numerous professional societies, including the American Federation for Clinical Research, American Society of Clinical Investigation, Infectious Diseases Society of America, British Society for Antimicrobial Chemotherapy, American Society of Microbiology, American College of Physicians, and the American Association for the Advancement of Science. Dr Andriole is the 1998 recipient of the Bristol Award of the Infectious Diseases Society of America; 1998 recipient of the Garrod Award from the British Society for Antimicrobial Chemotherapy; 1999 election as ‘Fellow’ by the American Association for the Advancement of Science for lifetime achievements in science and education. He is also the recipient of the Yale Department of Medicine Teacher of the Year Award and the Laureate Award from the American College of Physicians. In addition, he served as Councilor, Secretary, Vice-President and President of the Infectious Diseases Society of America.

Dr Andriole has authored more than 300 publications and is currently a member of the editorial boards of the Journal of Antimicrobial Chemotherapy, Diagnostic Microbiology and Infectious Disease, and is Editor of Current Opinion in Infectious Diseases, and is past Editor of Mediguide to Infectious Diseases and Cliniguide to Fungal Infections. He is also a peer reviewer for numerous journals, including the New England Journal of Medicine, American Journal of Medicine, Annals of Internal Medicine, Journal of Infectious Diseases/Clinical Infectious Diseases and Antimicrobial Agents and Chemotherapy.

Roger G. Finch

Professor Roger Finch is Professor of Infectious Diseases at the University of Nottingham and Consultant Physician to the City Hospital, Nottingham and is Chairman of the NeLCD Advisory Committee. He graduated from the University of Birmingham and has held Postgraduate appointments at the Universities of Bristol and London and also in the United States.

Professor Finch has authored more than 290 papers covering the fields of antimicrobial chemotherapy, lower respiratory tract infections and the pathogenesis of staphylococcal disease. He is currently European Editor of Current Opinion in Infectious Diseases and was formerly Editor-in-Chief of the Journal of Antimicrobial Chemotherapy as well as serving on the editorial boards of several international Infection journals. He has published several books and is co-editor of the reference work Antibiotic and Chemotherapy (8th Edition).

Professor Finch was formerly Chairman of the Working Party on Clinical Evaluation of Antibacterial Drugs,
member of the European Working Party on Clinical Trials of Anti-infective Agents and Co-Chairman of the Working Party on Self-medication of antibacterials without prescription. He was formerly President of the British Infection Society, Chairman of the Federation of Infection Societies and subsequently President of the European Society of Clinical Microbiology and Infectious Diseases. He serves on several committees of the Department of Health dealing with antibiotic resistance. He is advisor to the European Commission and the Committee on Proprietary Medicinal Products.

Section Editors

**Martin Fisher**

Dr Martin Fisher is Consultant Physician in HIV and Genitourinary Medicine at Brighton and Sussex University Hospitals, Brighton, UK. After graduating from Guys Hospital, London University, he trained in HIV and Genitourinary Medicine at the Chelsea and Westminster and St Mary’s Hospitals in London before taking up his current post in 1995. In addition to his clinical interests in outpatient and inpatient management of HIV infection, he leads an active research team with numerous ongoing studies including novel antiretroviral therapies and strategies, primary HIV infection, HIV/STI interactions, adherence to anti-HIV therapies, and novel strategies to improve detection of HIV and STIs. He is an active member of the British Association for Sexual Health and HIV (BASHH), Secretary to the British HIV Association (BHIVA), and is the Convenor of the Diploma in HIV Medicine.

**Anton Pozniak**

Dr Anton Pozniak studied medicine at the University of Bristol and qualified as MBChB in 1979. He trained in genito-urinary medicine and HIV at Middlesex Hospital, London, UK. He worked as a consultant physician in Zimbabwe where he researched for his doctorate in TB/HIV and moved back to the UK in 1991. He ran the HIV unit at King’s College, London before moving to his current position as Consultant Physician/Senior Lecturer at the Chelsea and Westminster Hospital in 1998. He became a fellow of the Royal College of Physicians in 1996. Dr Pozniak is a life member of the British HIV Association where he has helped co-ordinate and write the British HIV Association (BHIVA) anti-viral HIV guidelines and is chair of the TB/HIV guidelines committee. He was an advisor on HIV and AIDS to the UK Government Health Select Committee. He is a member of the UK Governments Expert Advisory Group on AIDS and on the executive of the European AIDS Clinical Society. He is on the Scientific Advisory Board of the Charity LEPRa and is a trustee of the Terence Higgins Trust, the UK’s largest HIV charity.
EDITORIAL COMMENT

Preexposure prophylaxis for HIV infection: it’s not as easy as ABC
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Abbreviations

FTC emtricitabine
PEPSE postexposure prophylaxis following sexual exposure
PREP preexposure prophylaxis
TDF tenofovir disoproxil

Despite the scientific awareness of proven strategies to prevent onward transmission of HIV, it is clear that there is significant ongoing transmission of the virus: it is estimated that 4.1 million adults and children were newly infected during 2005/2006 (Report on the global HIV epidemic; http://data.unaids.org/pub/GlobalReport/2006).

It is increasingly apparent that the prevention message of ‘ABC’ – abstinence, be faithful, condomize – is insufficient to overcome the complex psychosocial circumstances that result in risk of HIV infection. Alternative methods are increasingly being studied including male circumcision; reviewed in this section by Thomas Quinn (pp. 33–38); postexposure prophylaxis, reviewed in this section by Michelle Roland (pp. 39–46); vaccines; microbicides; and preexposure prophylaxis (PREP).

These methods recognize that condom use may be suboptimal for a variety of reasons (including availability, cost, religious barriers, and coercion) and – particularly in the case of microbicides and PREP – that a female-led method of HIV prevention may be of greater benefit than the traditional male-led method (i.e. condoms), given the increasingly changing epidemiology of HIV infection.

The concept of PREP – taking an anti-infective therapy prior to exposure to a pathogen – is not in itself novel. This concept has been widely used in prophylaxis against opportunistic infections in the context of HIV infection, as well as more widely in infectious diseases such as malaria, influenza and rheumatic fever.

The putative effectiveness of PREP for HIV has been studied in animal models of sexual transmission of HIV. These studies have aimed to demonstrate proof-of-concept that the use of antiretroviral therapy can reduce the likelihood or rate at which HIV infection (or equivalent) occurs after exposure. The only published data thus far [1], using tenofovir alone, showed that infection was delayed but not prevented. Preliminary results of these animal model studies (Heneine, presented at the 1st International Workshop on HIV Transmission; 11–12 August 2006; Toronto, Ontario, Canada) suggest that efficacy may be greater with emtricitabine (FTC), the combination of tenofovir disoproxil (TDF) and FTC, and intravenous TDF and FTC. Whilst animal model studies are limited by nature and have thus far predominantly used a rectal exposure methodology (which may not reflect the reality of exposure in the context of heterosexual HIV exposure in humans), they clearly justify the need for larger human studies.

In response to this perceived need and somewhat encouraging animal studies, multiple large-scale human studies have been planned and commenced across the globe. The primary outcomes of these studies are either safety or efficacy, and they have targeted different high-risk groups: men who have sex with men, intravenous drug users, commercial sex workers, and high-risk heterosexual women. Of the nine studies initially planned, four have already been discontinued either prior to or shortly after commencement. The reasons for discontinuation have been varied and include the inability to provide antiretroviral therapy should HIV infection occur, concerns about reduction in risk-behaviour counseling, the inability to afford PREP should it be shown to be effective, and concerns about the medical and laboratory conduct of trials. Five studies have, however, either commenced or are about to commence, in Africa, South America, USA and Thailand, and results will be reported between 2006 and 2009.

Multiple concerns about PREP remain, including the risk of toxicity secondary to PREP therapy, infection with resistant virus, cost-effectiveness, and the potential impact on risk behaviour (predominantly sexual activity) and ‘condom displacement’, i.e. a lessened perception of the need for (proven) barrier methods of HIV prevention that might result at a population level in increased rates of HIV transmission.

On the background of these justifiable concerns, the preliminary results of the first randomized study of PREP are encouraging (Peterson et al., presented at the XVI International AIDS Conference; 13–18 August 2006;
Toronto). This study (TDF versus placebo), of high-risk women in Ghana, Cameroon, and Nigeria, was powered only to look at toxicity and suggested no increased risk of drug-associated toxicity with TDF compared with placebo. Whilst there were less seroconversions in the treatment arm, this did not achieve statistical significance — nor was it powered to investigate this. Those who are ‘pro’ PREP may argue that the number of seroconversions was greater in the placebo arm; those who are ‘anti’ PREP may argue that seroconversions did occur despite prophylaxis. Evidently, there is a need to await the formal results and those of the larger ongoing studies that are powered to consider efficacy. Arguably the most provocative finding of this study was that risk behaviour ‘improved’ during the conduct of the study: the number of new sexual partners and number of partners were reduced, and the use of condoms increased. Of the seroconversions in TDF recipients, thus far no resistance was detectable, consistent with the animal studies that have suggested no TDF-associated mutations when infection has occurred despite prophylaxis.

Whilst the above study suggested no deleterious effect of PREP on sexual risk-taking behaviour, it is notable that the initial study of male circumcision as a method of HIV prevention [2] showed that there was some suggestion of increased risk taking (number of sexual partners). In the current era of understanding, there remains an equipoise as to whether these interventions affect transmission or not. If a beneficial effect is subsequently noted, this equipoise will be lost and it will therefore be difficult to extrapolate from such randomized studies to future risk taking after implementation: i.e. although the current data suggest no increased risk taking in the context of a PREP study, if PREP is shown to be effective and it were introduced in clinical practice, the impact on behaviour might be different. Whilst such an impact on behaviour has not so far generally been seen with postexposure prophylaxis [3], this remains of significant concern and requires prospective study should implementation occur.

Early cost-effectiveness modeling studies (Hill et al., presented at the 13th Conference on Retroviruses and Opportunistic Infections; 5–8 February 2006; Denver, Colorado, USA) have suggested that PREP may be cost-effective if used in high-risk populations, but sensitivity analyses will need to consider whether this is affected by any behaviour alteration as a result of efficacy and availability.

Further issues that will affect the efficacy of PREP in the ‘real world’ include awareness and applicability. Experts recognize that awareness of PEPSE (postexposure prophylaxis following sexual exposure) may be low even amongst high-risk groups, and the same is likely to be greater with PREP. Furthermore, even if awareness is raised, this does not ensure subsequent uptake. With PEPSE, for example, even if individuals are aware of its potential role after exposure, uptake is limited (Weatherburn et al., presented at the XVI International AIDS Conference; 13–18 August 2006; Toronto). It is notable that in the first randomized controlled trial of PREP (Peterson et al., presented at the XVI International AIDS Conference; 13–18 August 2006; Toronto), over half of those screened did not subsequently participate due to a variety of reasons including subsequent nonattendance, previously undiagnosed HIV infection, and coexisting conditions (including pregnancy) that precluded PREP use.

The potential use of PREP therefore needs to be considered within the overall context of HIV transmission and other prevention strategies. If PREP is shown to be effective it will need to be placed as part of a ‘menu’ that includes other clearly proven methods of prevention — condom use, abstinence, or reduced risk activity — and alongside other newer methods — such as circumcision, microbicides, vaccines, and highly active antiretroviral therapy (for which there is clear biologic plausibility and increasing cohort study evidence [4] (Kavitenkore et al., presented at the XVI International AIDS Conference; 13–18 August 2006; Toronto) to suggest that antiretroviral therapy per se may be effective in reducing HIV transmission).

It is highly unlikely that any individual method will be the panacea of HIV prevention. Should PREP be demonstrated as effective in any of the ongoing studies, careful monitoring of postintroduction effects (including risk behaviour and cost-effectiveness) will be essential. PREP must not be seen in isolation as a method of prevention without considering the overall effects on public as well as individual health.

References
HIV and malaria: interactions and implications
Laurence Slutskera and Barbara J. Marstonb

Purpose of review
This review summarizes accumulating evidence of interactions between HIV and malaria and implications related to prevention and treatment of coinfection.

Recent findings
HIV-infected persons are at increased risk for clinical malaria; the risk is greatest when immune suppression is advanced. Adults with advanced HIV may be at risk for failure of malaria treatment, especially with sulfa-based therapies. Malaria is associated with increases in HIV viral load that, while modest, may impact HIV progression or the risk of HIV transmission. Cotrimoxazole prophylaxis greatly reduces the risk of malaria in people with HIV; the risk can be further reduced with antiretroviral treatment and the use of insecticide treated mosquito nets. Increased numbers of doses of intermittent preventive treatment during pregnancy can reduce the risk of placental malaria in women with HIV.

Summary
Interactions between malaria and HIV have important public health implications. People with HIV should use cotrimoxazole and insecticide treated mosquito nets. Malaria prevention is particularly important for pregnant women with HIV, although more information is needed about the best combination of strategies for prevention. In people with HIV, malaria diagnoses should be confirmed, highly effective drugs should be used for treatment, and possible drug interactions should be considered.

Keywords
antiretroviral therapy, cotrimoxazole prophylaxis, HIV, insecticide-treated mosquito nets, intermittent preventive treatment, malaria

Introduction
Plasmodium falciparum malaria and HIV both cause substantial morbidity and mortality, particularly in sub-Saharan Africa. Given the extensive overlap in the geographic distribution of these two agents, even modest interactions between them would have enormous public health importance (Fig. 1).

Early studies failed to identify important interactions between malaria and HIV [1,2], but more recent evidence clearly supports the presence of significant impacts of each infection on the other. We review the evidence for interaction between P. falciparum infection and HIV, and the implications for prevention and treatment of malaria and HIV-related disease.

Overview of epidemiology
Each year, there are an estimated 300–500 million clinical cases of malaria globally, resulting in over 1 million deaths, most of them in young children in Africa [3]. Four species of malaria parasites can infect humans, but P. falciparum is by far the most important in terms of morbidity and mortality, and the most common in sub-Saharan Africa.

The clinical syndromes caused by malaria vary depending upon whether a patient comes from an area with stable endemic malaria transmission or unstable (infrequent or very low) transmission [4]. In areas where transmission is stable, the disease affects children and adults in different ways. Young children (under 5 years) experience chronic infections with recurrent parasitemia resulting in severe anemia and often death. Those who survive repeated infections acquire partial immunity by the age of 5 and carry it into their adult lives. Adults in stable endemic areas usually experience asymptomatic or milder infections.

In unstable transmission areas, immunity is not acquired. In these areas, the overwhelming clinical manifestation is acute febrile disease which can result in cerebral malaria, affecting persons of all ages.
Among adults, malaria is particularly problematic in pregnant women. Pregnant women in areas of unstable transmission may experience acute malaria, loss of pregnancy, still birth, and abortions. In more stable transmission areas, acquired immunity may be partially lost in pregnant women, who usually experience asymptomatic infections but can develop placental malaria that contributes to intrauterine growth retardation, low birth weight, and the concomitant risk of increased infant mortality.

HIV currently infects approximately 40,000,000 people, two-thirds of whom also reside in sub-Saharan Africa [5]. HIV disease continues to devastate, but recent years have...
seen some encouraging trends in the incidence of infection in some countries \[6,7\] and an increase in the numbers of people in sub-Saharan Africa who are able to access treatment \[8\].

The typical distribution of the diseases differs in important ways. Malaria is most common in rural areas, with the greatest disease burden borne by pregnant women and young children. In contrast, HIV rates are generally highest in urban areas, and are usually highest among young adults \[5\].

There are several ways that malaria and HIV could potentially interact, with effects upon transmission, clinical manifestations, and treatment outcomes of either disease (Fig. 2). In addition, there are potential interactions and convergent toxicity between the drugs used to treat each disease.

**Impact of HIV on malaria parasitemia and clinical severity in adults and children**

HIV disease impairs the acquired immunity to malaria seen in older children and adults in endemic areas. Large cohort studies in rural Uganda and Malawi have provided evidence of increased frequency (with rates one to two-fold higher) of both parasitemia and clinical malaria in HIV-infected adults, with increasing risk and higher density parasitemia associated with more advanced immunosuppression \[9,10\]. In Malawi, rates of malaria were increased among individuals with HIV, but not to the degree of increase seen for classic opportunistic infections like tuberculosis and *Pneumocystis jiroveci* pneumonia \[11\].

A recent prospective cohort study in South Africa evaluated whether HIV infection increased the risk of severe malaria in adults from both areas of stable and of unstable transmission \[12\]. Among 336 patients, 32 (10%) had severe malaria. The HIV prevalence was 33%, and 111 patients (33%) were nonimmune (from areas with unstable malaria transmission). In a multivariate analysis, HIV-infected nonimmune adults were at increased risk of severe malaria, and the risk was associated with a low CD4+ T-cell count. Nonimmune HIV-infected patients were significantly more likely to have severe clinical malaria than were nonimmune patients without HIV [odds ratio (OR) 4.15; 95% confidence interval (CI) 1.57–10.97; \(P = 0.003\)]. In another study in an area of South Africa with unstable malaria transmission \[13\], HIV-infected adults with malaria were significantly more likely to die, or require an intensive care unit admission than those with malaria without HIV \[13\]. In contrast, HIV infection did not confer an increased risk of these severity measures in partially immune adults from areas with more stable transmission \[9\].

In children, the situation is more complicated. Early prospective evaluations of HIV-infected infants did not demonstrate an increase in frequency or density of parasitemia associated with HIV infection \[14,15\]. In a recent
HIV is associated with an increased risk of placental malaria [23] and associated adverse fetal outcomes including low birth weight [24]. The administration of a full treatment dose of an effective antimalarial drug at predefined gestational intervals (intermittent preventive treatment in pregnancy; IPTp) reduces the risk of placental malaria; sulfadoxine–pyrimethamine is the recommended drug for IPTp. In a clinical trial in western Kenya, HIV-infected primigravidae and secundigravidae required at least three doses to achieve a reduction of placental parasitemia similar to that seen in HIV-negative women receiving two doses of sulfadoxine–pyrimethamine [25]. A recent study in Malawi [26*] confirmed that monthly sulfadoxine–pyrimethamine (median three doses) was more effective at reducing rates of placental parasitemia than two-dose regimens, in women with and without HIV. The study was not powered to demonstrate changes in fetal outcomes, but did show a reduction in clinical malaria (defined by fever and parasitemia), particularly among women with HIV.

Impact of malaria on HIV
As occurs with tuberculosis and other major opportunistic infections, malarial episodes can transiently increase viral load, and thus could theoretically have an impact on HIV disease progression and HIV transmission. In a study from Malawi [28*], asymptomatic malaria infection was associated with an increase in HIV viral load of 0.25 log overall, and up to about 0.89 log when fever and parasite density was over 2000 parasitemia/μl. Viral loads returned to baseline about 8–9 weeks following effective antimalarial treatment. The clinical relevance and long-term impact of these short-term changes is not clear, particularly in individuals. Mermin et al. [29] recently reported an association between malaria infection and decline in CD4 cell count, but a causal relationship was not established.

In pregnant women, recent studies have also confirmed that malaria parasitemia was associated with increased HIV concentrations, with a magnitude similar to that...
observed in asymptotically infected nonpregnant adults [30]. One study also assessed the relationship between placental malaria and placental viral load and found that malaria was associated with an overall twofold increase in placental HIV concentrations, with the greatest increase among women with higher placental densities [31].

Placental malaria has also been associated with increased expression of CCR5 receptors in placental macrophages, raising the possibility of placental malaria leading to increased mother to child transmission (MTCT) of HIV [32]. The data concerning the impact of malaria during pregnancy on the risk of MTCT of HIV, however, are conflicting. A study from Uganda [33] demonstrated increased MTCT in women with placental malaria, but studies from Kenya did not show this association [34,35].

Malaria has an important indirect effect on the risk of HIV transmission, because anemia caused by \textit{P. falciparum} remains a frequent cause of blood transfusions. This relationship was documented 20 years ago in the Democratic Republic of Congo (then Zaire); 70% of children hospitalized for malaria were transfused, and there was a strong dose response between transfusions and HIV risk [1,36]. Improved blood collection and testing practices are leading to improved transfusion safety in Africa [37,38], but few countries there are yet practicing universal screening of blood. Efforts must continue to reduce the risk of malaria and malaria-related anemia to prevent unnecessary transfusions, and to continue to improve the safety of the blood supply.

\section*{Prevention of malaria in people with HIV}

Approaches to prevention of malaria and malaria-related morbidity and mortality include vector control, prophylaxis, and IPTp. Bednets or curtains treated with insecticides (ITNs) significantly reduce the risk of mortality in children in Africa [39], including studies in areas where HIV prevalence is high [40]. Cotrimoxazole effectively prevents malaria in HIV-negative children [41], and marked reduction in malaria incidence is an important component of the decline in rates of illness seen in Africans with HIV who receive cotrimoxazole [16,42,43]. Cotrimoxazole and sulfadoxine–pyrimethamine, both antifolate drugs, share mechanism of action, adverse event profiles, and molecular markers of drug resistance. Due to the reduction in rates of malaria among HIV-infected Africans taking cotrimoxazole, however, in these studies cotrimoxazole reduced the overall burden of sulfas-resistant \textit{P. falciparum} infection [43]. A recent report suggested that cotrimoxazole prophylaxis may be associated with higher risks of sulfadoxine–pyrimethamine treatment failure in children (RR 1.77; 95% CI 1.04–3.05) and adults (RR 2.05; 95% CI 0.8–5.0) [44].

In Africa, because cotrimoxazole has been shown to effectively reduce the risk of HIV-associated opportunistic infections and mortality, even in areas where rates of antibiotic resistance are high, it is now strongly recommended for people with symptomatic HIV disease [45].

A recent study of HIV-infected individuals in Uganda demonstrated that malaria burden was reduced by 70% with cotrimoxazole, was then reduced a further 50% when antiretroviral drugs were provided, and finally a further 50% with provision of ITNs [46**].

Broad administration of cotrimoxazole to individuals with HIV raises some important considerations. The relatively high rates of nonmalaria causes of fever in people with HIV, combined with a reduction in malaria risk with cotrimoxazole prophylaxis, strongly suggest that presumptive therapy for malaria should be avoided in HIV-infected African adults or children with HIV on cotrimoxazole prophylaxis. Careful evaluation for other causes of fever should be combined with specific diagnostic testing for malaria.

In HIV-infected pregnant women in Lusaka, Zambia, cotrimoxazole was shown to have substantial beneficial effects [47]. Malaria transmission in Lusaka is low, however, suggesting the observed benefit was not due to suppression of \textit{P. falciparum} infection. Moreover, the effect of cotrimoxazole on placental malaria has not been demonstrated. Due to concerns about adverse effects associated with administration of sulfa drugs to people with HIV already on cotrimoxazole, the World Health Organization (WHO) has recommended that sulfadoxine–pyrimethamine-based IPTp should be avoided in HIV-infected pregnant women receiving cotrimoxazole [45,48]. A key research priority should be to evaluate the impact of routine cotrimoxazole prophylaxis on placental malaria and rates of associated adverse birth outcomes in women with HIV.

Additionally, while cotrimoxazole effectively prevented malaria in HIV-negative children in Mali [41], and malaria rates were reduced during the period following introduction of cotrimoxazole in HIV-infected children in Uganda [16], the recommendation for cotrimoxazole prophylaxis for HIV-infected children is based primarily on reduction in pneumonia rates [49]. There is a need to further evaluate the impact of cotrimoxazole prophylaxis on malaria in children with HIV.

\section*{Other drug issues}

The expanding use of antiretroviral drugs could have implications for malaria control because of the possible direct effects of these drugs on \textit{P. falciparum} and because of improvement in immune status. Indeed, most of the HIV protease inhibitors have antimalarial activity,
possibly at clinically relevant concentrations [50]. HIV protease inhibitors, however, have yet to show any demonstrable clinical impact on malaria and, as expensive second-line drugs, are still not commonly used in malaria-endemic areas. Of interest, treatment with antiretrovirals (primarily nonnucleoside reverse transcriptase inhibitors; NNRTIs) in Uganda was associated with decreased malaria incidence, but this may have been due to immune reconstitution rather than specific antimalarial activity [46**].

Conversely, some antimalarial drugs may have direct anti-HIV activity. For example, chloroquine has demonstrated modest anti-HIV efficacy [51]. Due to widespread chloroquine-resistant \textit{P. falciparum}, however, this drug is no longer commonly used for treatment.

There are a number of potential drug interactions between antimalarial and HIV drugs. For example, ritonavir or lopinavir/ritonavir may boost levels of quinine or lumefantrine, perhaps to dangerous levels, while NNRTIs such as nevirapine may lower the concentrations and effectiveness of these drugs. The balance between artemether and its metabolites may also be impacted by protease inhibitors or NNRTIs, but the data are still limited and the clinical implications are unclear [52].

Drug toxicity may also complicate the clinical comanagement of HIV and malaria. For example, a common side effect of zidovudine is anemia, which is an obvious concern in patients who may be anemic due to malaria. Another issue is the convergent toxicity of nevirapine-based antiretroviral therapy and sulfadoxine–pyrimethamine, particularly in pregnant women who are taking or have taken IPTp. Hypersensitivity reactions to nevirapine, including potentially fatal liver and skin reactions, are fairly common and clinically indistinguishable from reactions to sulfadoxine–pyrimethamine. Staggering the introduction of these drugs during pregnancy may help to reduce the risk of adverse events [53].

**Conclusion**

Interactions between malaria and HIV have important public health implications for both individuals and HIV and malaria control programs. HIV-infected individuals should receive cotrimoxazole as appropriate [45] and should be targeted for specific malaria prevention interventions such as insecticide-treated nets for those living in endemic areas and antimalarial chemoprophylaxis for (nonimmune) persons traveling to endemic areas. Given the high efficacy of cotrimoxazole to prevent malaria infection, cotrimoxazole-treated patients presenting with fever may be much less likely to have malaria, and may warrant a more detailed diagnostic evaluation; for those on cotrimoxazole prophylaxis who do develop malaria, chosen antimalarial treatment regimens should not be sulfadoxine–pyrimethamine for IPTp.

Studies are urgently needed to determine the optimal approach to fever diagnosis and management in people with HIV on cotrimoxazole in resource limited settings.

Drug interactions for patients on antiretrovirals and antimalarials need to be considered; and patients with advanced HIV need prompt and effective antimalarial treatment. There is a need for studies of the effectiveness of ACTs in people with advanced HIV.

Finally, there is a clear need for coordination between HIV and malaria control programs. Malaria control programs should specifically consider malaria prevention interventions for people with HIV, and HIV prevention and treatment programs should consider the possibility of taking advantage of contacts with healthcare systems to deliver malaria prevention interventions. Laboratories should be strengthened to enhance laboratory diagnostic capacity for both diseases, and interventions in orphan and child support programs and general medical, antenatal and maternal health settings should be seamlessly coordinated.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 91–92).


This study also adds to the evidence that adults with HIV are at higher risk for malaria than those without HIV, but demonstrates that the increase in disease risk for malaria is not as great as for classical opportunistic infections like tuberculosis.

This paper provides evidence that HIV-infected patients from areas with low or unstable malaria transmission are at higher risk of severe malaria than HIV-positive patients from areas with more stable malaria transmission.

This study demonstrates sustained increases in HIV viral load associated with malaria infection. Although these increases were relatively modest, they may have important public health implications because of the very large numbers of people affected by both malaria and HIV.

This paper provides evidence that the burden of malaria disease in HIV-infected adults in South Africa is not as great as for classical opportunistic infections like tuberculosis.

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HIV infection and AIDS


HIV and pneumococcal disease
Keith P. Klugmana,b, Shabir A. Madhi b and Charles Feldman c

Purpose of review
To describe the impact of highly active antiretroviral therapy on the burden of pneumococcal disease and advances in our understanding of the impact of HIV on this disease.

Recent findings
Although highly active antiretroviral therapy has reduced the burden of pneumococcal disease among HIV-infected adults, these infections remain far more common than in HIV uninfected adults. HIV-infected adults who smoke or have comorbidities are at particular risk. In the absence of highly active antiretroviral therapy, pneumococcal meningitis has emerged in Africa as a major disease burden with a high mortality among HIV-infected children and adults. Conjugate pneumococcal vaccine protects HIV-infected infants from pneumococcal pneumonia. In the United States, where conjugate vaccine is given to children, herd immunity has reduced the burden of invasive pneumococcal disease among HIV-infected adults.

Summary
The pneumococcus remains a significant cause of morbidity and mortality among HIV-infected children and adults, both in developed and in developing countries.

Keywords
HIV, meningitis, pneumococcus, pneumonia

Introduction
Acute respiratory infections are the leading infectious causes of death in both children and adults. Among HIV-infected people, the burden of these infections is greatly increased, and particularly in developing countries with little access to highly active antiretroviral therapy (HAART), the burden of pneumococcal disease falls disproportionately on the HIV-infected population. This review describes the significant remaining burden of pneumococcal disease in the HAART era, new insights into pathogenesis of pneumococcal disease in HIV-infected persons, and the impact of HIV on pneumococcal disease, antimicrobial resistance and vaccination.

Burden of disease and impact of highly active antiretroviral therapy
The burden of invasive pneumococcal disease in African HIV-infected children less than 2 years of age (3036 per 100 000) was 42-fold (95% confidence interval (CI) 27–66) greater than that in HIV-uninfected children in the pre-HAART era [1]. In the USA, the burden of invasive pneumococcal disease was 9–13-fold greater in HIV-infected children (incidence 11 300–12 240 per 100 000 person years) prior to the introduction of HAART [2,3]. The apparently greater absolute disease incidence in the US is likely to be a measure of the greater likelihood of febrile children in the US getting a blood culture.

Similarly high rates of pneumococcal bacteremia existed in adults living with AIDS in the US prior to the introduction of HAART (1094/100 000 in 1995/6) was 42-fold (95% confidence interval (CI) 27–66) greater than that in HIV-uninfected children in the pre-HAART era [1]. In the USA, the burden of invasive pneumococcal disease was 9–13-fold greater in HIV-infected children (incidence 11 300–12 240 per 100 000 person years) prior to the introduction of HAART [2,3]. The apparently greater absolute disease incidence in the US is likely to be a measure of the greater likelihood of febrile children in the US getting a blood culture.
(adjusted OR 5.28), prior hospitalization (adjusted OR 3.38), current smoking (adjusted OR 5.19), and CD4 cell count lower than 100 cells/µl (adjusted OR 2.38). Use of HAART (adjusted OR 0.37) and pneumococcal vaccine (adjusted OR 0.39) were protective factors [5*]. Risk factors and prognosis of pneumococcal bacteremia in the HAART era are thus more similar than previously to those reported in non-HIV-infected individuals.

**Pathogenesis of pneumococcal infections in HIV-infected patients**

To better understand why HIV-infected adults have an increased susceptibility to pneumococcal disease, an in vitro study was undertaken to demonstrate whether impaired cytokine release from alveolar macrophages of HIV-infected patients occurred in response to *Streptococcus pneumoniae* challenge [6*]. The investigators documented that interleukin (IL)-1, 6 and 8 increased in both the HIV-infected and uninfected groups following challenge, but whereas IL-1 and IL-6 were higher in the HIV-infected group, the IL-8 levels were significantly lower. The authors suggest that the reduced IL-8 may result in impaired neutrophil recruitment, thereby increasing the susceptibility of HIV-infected patients to pneumococcal infections.

**Pneumococcal pneumonia**

Community-acquired bacterial pneumonia occurs less frequently in HIV-infected patients initiated on a protease inhibitor-containing antiretroviral regimen [7*]. In a follow-up period of 43 months, 29 cases of pneumonia were documented in the antiprotease cohort (APROCO) in France, giving an incidence of 800/100,000 patient-years. Of the 11 definitive cases, nine were due to *Streptococcus pneumoniae*, one to *Legionella pneumophila* and one to *Haemophilus influenzae*. The occurrence of bacterial pneumonia was associated with various host factors including older age, smoking, presumed HIV infection through injecting drug use, and factors associated with lower virological efficacy of antiretroviral therapy.

Nosocomial bacterial pneumonia has been considered to be an important cause of morbidity and mortality among patients with advanced AIDS, but has declined in incidence since the introduction of HAART [8*]. A retrospective study of all HIV-infected patients admitted to the Infectious Disease Clinic in Milan between 1988 and 2002 was undertaken [8*] in which investigators identified 120 episodes of nosocomial bacterial pneumonia, of which 21% were due to *Streptococcus pneumoniae*. The overall mortality rate for the nosocomial bacterial pneumonias was 25.8% and the only independent predictor of mortality was the presence of methicillin-resistant *Staphylococcus* as the cause.

**Pneumococcal meningitis**

In sub-Saharan Africa the burden of HIV among patients with meningitis is considerable, and is associated with an extreme level of mortality. Among adults in Malawi with meningitis, 158 out of 167 patients consenting to testing (95%) were HIV positive [9]. Inpatient mortality was 65% for pneumococcal meningitis. The remaining 35% of hospital survivors were followed for a median of 414 days, and 39% of these patients died in the community during the study period. Among children, 62 (42.2%) of 147 with meningitis in Soweto tested for HIV-1 infection were infected [10]. *S. pneumoniae* exceeded *H. influenzae* type b (Hib) as the most important cause of meningitis in HIV-1-infected (74.2% versus 12.9%, respectively) compared with uninfected children (29.4% versus 42.3%, respectively; *P < 0.00005*) even prior to the introduction of Hib conjugate vaccines. The estimated relative risk of pneumococcal meningitis was much greater in HIV-1-infected [relative risk (RR) 40.4; 95% CI 17.7–92.2] than in uninfected children under 2 years of age. HIV-1-infected children had a higher rate of morbidity or mortality (60.8% versus 36.0%, respectively; *P = 0.04*).

**Antibiotic resistance**

The unusual occurrence of an altered penicillin binding protein PBP 2A associated with β-lactam resistance was reported in an HIV-seropositive child with recurrent pneumonia in whom three identical *S. pneumoniae* serotype 14 isolates were cultured sequentially [11*]. The third isolate showed a decrease in penicillin, cefotaxime and ceftriaxone resistance compared with isolates 1 and 2, associated with replacement of an altered PBP 2A with a wild type PBP 2A. Interestingly, faster growth rates and larger capsules were seen in isolates 2 and 3 compared with isolate 1, suggesting that these events produce a strain which evolved into a fitter and more virulent type, albeit less antibiotic resistant, which ultimately led to the child’s death.

For some years it has been known that pneumococci causing invasive disease among HIV-infected adults [12] and children [1] are more resistant to antibiotics. The preponderance of pediatric serotypes among HIV-infected adults (see below) may be a factor that increases the resistance of strains isolated from HIV-infected adults, as may exposure to antibiotics as therapy or prophylaxis. Of particular concern is the impact of trimethoprim–sulfamethoxazole prophylaxis on susceptibility of the pneumococcus to that drug, and the role of trimethoprim–sulfamethoxazole in selecting multiply resistant pneumococci. Children on prophylaxis have been shown to be more frequently colonized with drug-resistant strains of pneumococci [13] and more likely to develop invasive disease associated with more highly resistant strains [1]. The rates of resistance to
trimethoprim–sulfamethoxazole are high in many African countries. No impact of prophylaxis could be found on pneumococcal disease in Uganda in a setting of 70% resistance to the drug [14], so reductions in pneumonia incidence may not be primarily due to reductions in pneumococcal disease. Cotrimoxazole prophylaxis was, however, associated with a 63% reduction in hospitalization for pneumonia, of unknown etiology, among African children from an area with a high prevalence of \(S. \text{pneumoniae} \) resistance to cotrimoxazole [15]. There is indirect evidence that cotrimoxazole prophylaxis may reduce bacterial infections (26.8% versus 11.3%), especially due to \(S. \text{pneumoniae} \), although the susceptibility of the pathogens was not reported in that paper.

An investigation was undertaken in Kenya of 162 upper respiratory tract isolates from 104 HIV-infected adults and 46 children enrolled in a cotrimoxazole prophylaxis study [17]. Levels of antibiotic resistance were very high [152 isolates were cotrimoxazole nonsusceptible (134 fully resistant) and 124 intermediate-resistant to penicillin]. Resistance was noted among a number of different serotypes, 15 of which have never or rarely had documented resistance to penicillin, including serotypes 3, 4, 7C, 10A, 11A, 13, 15A, 16F, 17F, 19B, 21, 35A, and 35B. Limited \(\text{pfp2b} \) and \(\text{dhfr} \) sequence analysis documented that the majority of clones contained alleles that were very different from other known resistance containing \(\text{pfp2b} \) and \(\text{dhfr} \) genes, although they did contain the same key codon substitutions required for resistance.

**Pneumococcal vaccines**

Case control studies among HIV-infected people in developed countries who have access to antiretrovirals have generally shown protection from invasive disease among those who have received the 23-valent pneumococcal vaccine (PPV) as mentioned above. The only randomized trial of this vaccine among HIV-infected people without access to antiretrovirals showed an increase in pneumonia among vaccinees (40 episodes versus 21; hazard ratio 1.89; 95% CI 1.1–3.2), and a 6-year follow-up of that study showed no further increase in pneumonia but a paradoxical significant 16% reduction in mortality in the vaccinated group [14]. The issue of the usefulness versus the risk of polysaccharide vaccine in Africa thus remains unresolved.

The immunogenicity of a 7-valent conjugate pneumococcal vaccine (CPV) was studied in the original study cohort of HIV-infected Ugandan patients described above with the administration of two doses of CPV to 54 past PPV recipients and 55 past placebo recipients [18]. Postvaccination anticapsular immunoglobulin G (IgG) concentrations were directly correlated with CD4 cell counts and there were significant increases in anticapsular IgG for all serotypes after the first dose and for all serotypes except 14 and 9V after the second dose, with no effect of past PPV on the vaccine response.

Conjugate pneumococcal vaccine given to HIV-infected children in infancy not only prevents 65% of vaccine type invasive infections by intent to treat analysis [19], but also reduces the burden of clinical pneumonia by an estimated 2573 episodes/100,000 children immunized per year [20**]. The vaccine also reduces the burden of antibiotic-resistant invasive infections in HIV-infected children [19].

Although the antibodies to pneumococcal capsules induced by CPV in HIV-infected infants are similar quantitatively to those induced in HIV-uninfected infants, recent data suggest that there are qualitative differences—these antibodies are less able to facilitate opsonophagocytosis of pneumococci than are those induced in HIV-uninfected children [21]. In symptomatic HIV-infected children there are both qualitative and quantitative reductions in antibody response to the pneumococcal conjugate [21*].

In populations where children receive CPV, there are data to suggest that the burden of pneumococcal disease due to the conjugate vaccine types may fall in HIV-infected adults through herd immunity. It has been known for some time that close exposure to children is a risk for pneumococcal bacteremia in HIV-infected adults [22] and that the pediatric serogroups of pneumococci are more commonly found in HIV-infected adults than in uninfected adults [12,23]. Young HIV-infected women are at particular risk for infection with pediatric serotypes [24]. Direct evidence for the impact of conjugate vaccine use in children on the burden of disease in adults is now available from a CDC study in which all invasive disease in HIV-infected adults post vaccine introduction decreased by 19% \(P=0.002 \) [25**] and pediatric conjugate vaccine serotypes were reduced by 62% \(P<0.001 \). Of concern, however, is the degree of replacement disease by nonvaccine serotypes that increased by 44% \(P<0.001 \) [25**].

**Invasive pneumococcal disease**

In a retrospective record review from the US, the demographic, clinical, laboratory, radiographic and microbiologic data were compared in 52 HIV-infected and 51 noninfected patients with invasive pneumococcal disease (IPD) [26*]. For that study the definition of IPD used was the isolation of \(S. \text{pneumoniae} \) from the blood, normal sterile fluids (e.g. cerebrospinal fluid or synovial fluid), abscess fluid from soft tissues or the respiratory tract of patients with signs, symptoms, and radiographic findings suggestive of a pulmonary infection. At the time of initial
presentation, the duration and severity of symptoms, signs, radiographic manifestations and laboratory abnormalities were generally similar in the two groups. There was a higher incidence of bacteremia among the HIV-infected group (77% versus 55%; \( P < 0.01 \)). There was a trend for the length of hospital stay to be shorter in these patients and less of the HIV-infected patients required admission to the intensive care unit or mechanical ventilation. Interestingly, the mortality of the HIV-infected patients was one-fifth of that of the patients that were not HIV infected. The authors suggested that the reasons for the lower mortality may be due to less advanced age and fewer comorbidities in the HIV-infected cases or possibly that the inflammatory response to IPD may be blunted in HIV-infected patients.

Conclusion

The pneumococcus continues to cause significant morbidity and mortality among HIV-infected individuals. Prevention efforts have reduced this burden by the introduction of HAART and by herd immunity of adults in communities where children receive conjugate pneumococcal vaccine. The impact of trimethoprim–sulfamethoxazole on pneumococcal disease may be frustrated by resistance emergence but more data are needed on the impact of resistance on the prophylactic, as opposed to the therapeutic, efficacy of this drug against resistant strains. The impact of polysaccharide pneumococcal vaccine on HIV-infected people not on HAART remains controversial, and research is needed on the impact of conjugate vaccine on adult disease, both by direct vaccination and by vaccinating children to induce herd immunity in developing countries.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

** of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 91).

This study from Spain shows that the residual cases of pneumococcal disease in the HAART era occur in patients with comorbidities in addition to HIV, such as lung disease and smoking. In a case–control analysis, both HAART and pneumococcal vaccine prevented IPD.
Selection of a pneumococcal strain with increased virulence and decreased antimicrobial resistance following repeated bacteremias in an HIV-infected child.


The management of HIV and hepatitis B coinfection
Gail Matthews

Purpose of review
Coinfection with HIV and hepatitis B virus has a significant impact on the natural history of hepatitis B disease with faster rates of progression to cirrhosis and end stage liver disease. An increasing number of hepatitis B virus active drugs are now available, many of which have dual anti-HIV activity. This review highlights the most important recent developments in the management of HIV and hepatitis B virus coinfection.

Recent findings
Natural history studies continue to confirm the increased rate of liver-related mortality in coinfected individuals and the importance of hepatocellular carcinoma in this population. The most recent studies of adefovir and tenofovir in open label use in coinfected individuals are discussed and new data on the activity of emtricitabine, entecavir and pegylated interferon are presented. Strategies for use of these new options for anti-hepatitis B virus therapy in coinfected individuals are discussed.

Summary
Prevention of end stage liver disease and hepatocellular carcinoma in the coinfected population is vital and the increasing availability of drugs with potent anti-hepatitis B activity is encouraging. Appropriate diagnosis and monitoring of hepatitis B, coupled with better understanding of the mechanisms of drug resistance, will enable clinicians to manage coinfection more effectively.

Keywords
antiviral therapy, hepatitis B, HIV

Introduction
Coinfection with hepatitis B virus (HBV) is estimated to occur with a prevalence of between 5 and 10% in most HIV-infected populations [1,2,3*]. This prevalence is considerably less than that of HIV and hepatitis C coinfection and demonstrates much less geographical variability, largely due to differences in the predominant routes of transmission. Despite the lesser burden of HIV/HBV related disease there is increasing awareness of the need to appropriately diagnose, assess and treat such individuals. Natural history studies continue to demonstrate the greater risk of liver disease progression in HIV/HBV coinfected populations. In addition, advances in the field of HBV monoinfection have resulted in a greater understanding of the mechanisms of HBV resistance, and an increasing number of new HBV-active drugs. This article aims to review the most recent data relevant to the care and management of patients with HIV and HBV coinfection.

Natural history of HIV and hepatitis B virus coinfection
In 2001 an analysis of the Multicentre AIDS Cohort Study (MACS) cohort demonstrated a clearly increased risk of liver-related mortality in HIV/HBV coinfected patients [1]. In 2005 the EUROSIDA study group [3**] further examined the effect of HBsAg positivity on progression to AIDS, death from all causes, liver disease related death and response to highly active antiretroviral therapy (HAART). Amongst 5728 HIV-positive individuals tested for hepatitis B surface antigen (HBsAg), 498 (8.7%) were HBsAg positive. The increased risk of liver disease related mortality was confirmed as threefold higher in HBsAg positive patients than in the HBsAg negative group. AIDS and AIDS-related deaths were similar between groups as were immunological and virological responses following HAART initiation. No reduction in liver-related deaths was observed with the specific use of HBV-active HAART in this study, although two other cohort studies have suggested that the use of (lamivudine-containing) HAART may reduce liver-related mortality in HIV/HBV coinfected individuals [4,5]. The lack of increased liver-related mortality following HAART initiation in EUROSIDA is reassuring with regard to the impact of immune reconstitution disease or lamivudine resistance flares on HBV disease progression. In addition, the finding of an association between CD4 cell increase after HAART and reduction in end-stage liver disease mortality supports the use of HAART in this setting.
The causes of liver-related mortality in HIV-positive individuals were evaluated in a recent study of 822 individuals from France [6]. In this cohort, liver disease accounted for one-fifth of all deaths: 88% of all liver related deaths were due to decompensated cirrhosis and 15% due to hepatocellular carcinoma (HCC). In HIV/HBV patients, however, HCC was the cause of liver-related death in 50% of cases, significantly greater than the proportion in HCV/HIV or HIV alone. The altered and aggressive presentation of HCC in the setting of HIV/viral hepatitis coinflection has also been reported in an Italian study [7]. These findings highlight the need for awareness and appropriate screening for hepatoma in the HIV/HBV coinfected population.

The impact of occult HBV in HIV/HBV coinfection, defined loosely as the presence of HBV DNA by sensitive polymerase chain reaction (PCR) in the absence of HBsAg positivity, has also been considered. A study of 115 antiretroviral naïve patients found approximately 20% of HBsAg negative patients to be HBV DNA positive on qualitative assay [8]. Following HAART initiation, hepatic flare was more frequent in those patients with occult HBV, suggesting a possible clinical relevance to this condition. This contrasts with a study from the Netherlands in which occult HBV was found in only 4% of patients, with no association with hepatic flare after HAART initiation [9]. Thus the true significance of occult HBV remains unclear.

In summary, these recent natural history studies confirm the importance of identifying HIV/HBV coinfected individuals and support the use of effective HAART and avoidance of significant immunosuppression in this group. The use of HBV active HAART is likely to be particularly beneficial and is discussed below.

**Lamivudine**

Since 1996 lamivudine has been extensively used for the treatment of both HIV and HBV in coinfected individuals. The high rate of resistance development when lamivudine is used as HBV monotherapy in this setting is well known. A recent publication from a collaborative group from Australia and the United States has extended this knowledge with a description of the prevalence and characteristics of lamivudine resistance in 81 HIV/HBV coinfected individuals [10]. This study documented an almost universal HBV resistance prevalence (94%) in viremic patients with more than 4 years lamivudine use and found evidence of a triple HBV mutational pattern in 17% of patients, twice that in HBV monoinfected patients. The significance of this mutation, and the implications and complexities of other patterns of HBV resistance, have been discussed in several recent review articles [11,12,13]. These papers highlight the importance of avoiding lamivudine monotherapy for HBV in coinfected individuals, now increasingly possible with the recent availability of at least three other HBV active drugs (see below).

**Tenofovir**

Tenofovir disoproxil fumarate (TDF) was licensed in 2001 for the treatment of HIV infection and subsequently has been widely used in HIV/HBV coinfected individuals. Although unlicensed as hepatitis B therapy, data from a subanalysis of HBV/HIV coinfected patients in the Gilead 903 and 904 studies [14], and data from open label use in HIV clinics [15–17], have confirmed its activity against HBV in both lamivudine naïve and lamivudine resistant patients. A report of its activity in one of the largest treated cohorts of 65 HIV/HBV coinfected individuals was recently published [18]. Over 12 months a median reduction in HBV DNA of 4.56 log10 copies/ml was observed in 54 hepatitis B e antigen (HBeAg) positive patients, with 30% achieving undetectable HBV DNA (<2.3 log10 copies/ml). In 11 HBeAg negative patients, who initiated therapy with a lower HBV DNA at baseline, 82% became HBV DNA undetectable. HBV DNA suppression occurred in both lamivudine naïve and lamivudine resistant individuals and no TDF-associated HBV mutations were observed, despite HBV rebound from nadir in two patients and nonresponse to TDF in four.

Although this study confirms the short-term potency and safety of TDF in a variety of patients, it is limited, as the authors point out, by its retrospective nature and the variability in monitoring of HBV-related parameters. Increasingly, however, attention is being focused specifically on the anti-HBV activity of TDF. A prospective study of the early HBV virological response in 28 TDF-treated HIV/HBV individuals examined factors predicting HBV DNA suppression [19]. In multivariate analysis only baseline HBV viral load and HBeAg positivity influenced HBV decay; HBV genotype, fibrosis score, pol mutations (YMDD mutant), HCV status and HIV parameters had no impact. In this study the use of TDF/lamivudine combination versus TDF monotherapy in lamivudine-resistant patients failed to show a benefit in greater HBV reduction. A further study [20] examining HBV viral kinetics in 13 patients on combination lamivudine/tenofovir demonstrated that HBV decline was similar in both wild type and lamivudine-resistant virus, confirming that TDF is equally effective in both situations. Further detailed analysis of both serum and intrahepatic HBV dynamics on treatment regimens in HIV/HBV coinfected individuals would be valuable.

Mutations associated with HBV resistance to tenofovir have now been reported [21]. In a study from Spain of 35 patients with detectable HBV on TDF, a mutation at rTA194T in the polymerase gene was discovered in two
patients, both with over 12 months of TDF exposure. *In vitro*, this new mutation conferred reduced susceptibility to TDF, particularly in the presence of lamivudine mutations. The significance of this mutation, however, remains to be determined as neither patient exhibited clinical resistance, and a subsequent study from Gilead Sciences [22] failed to show an association between this mutation and reduced susceptibility to TDF *in vitro*.

**Adefovir**

Although licensed for HBV therapy and widely used in HBV monoinfection, adefovir in HIV/HBV coinfection has generally been avoided, largely due to the availability of tenofovir in this setting. Tenofovir appears to have greater potency than adefovir [23], and is effective even in the situation of adefovir failure [24*,25]. Recently published data by Benhamou *et al.* [26**] on the 3-year follow-up of 35 lamivudine-resistant HIV/HBV coinfected patients treated with adefovir found that HBV decline was maintained through to week 144, with an overall median reduction in HBV DNA from baseline of 5.90 log10 copies/ml. No adefovir-associated HBV resistance mutations were identified, although only seven (25%) patients had undetectable HBV DNA by week 144. Similarly, the rtK65R or K70E changes seen in HIV-1 adefovir resistance were not observed, although the majority of patients were HIV-1 undetectable. Adefovir resistance is increasingly recognized in HBV treatment and HBV variants exhibiting primary adefovir resistance have recently been described [27*]. The absence of HBV resistance seen in this study contrasts with the incidence of adefovir resistance in HBV monoinfected patients, reported to occur in up to 18% of lamivudine resistant patients treated with adefovir alone [28]. The continuation of lamivudine with adefovir in the Benhamou study suggests that there may be a benefit to the use of combination therapy in delaying resistance. The absence of HIV resistance mutations is encouraging and is supported by other data recently published from Spain demonstrating no HIV mutations in seven adefovir-treated patients with actively replicating HIV over 48 weeks [29]. The development of two cases of HCC in the Benhamou study despite HBV virological suppression highlights the importance of this condition in HIV/HBV coinfection.

**Emtricitabine**

Emtricitabine (FTC) is a pyrimidine nucleoside analogue, similar in structure and activity to lamivudine, and approved by the US Food and Drug Administration (FDA) for treatment of HIV infection. Confirmation of its efficacy and tolerability, in combination with tenofovir as a nucleoside backbone, was reported in the Gilead 934 study in the *New England Journal of Medicine* in early 2006 [30*]. Although not officially approved for treatment of chronic hepatitis B, the similarity of FTC to lamivudine and data from phase 2 and 3 trials in chronic hepatitis B suggest that it is equally efficacious in HIV/HBV coinfection. In a trial of 167 therapy-naïve HBV monoinfected patients, FTC reduced HBV DNA to less than 400 copies/ml in 54% of patients, with a median reduction in HBV DNA of 4.5 log10 copies/ml by 48 weeks [31*]. Anti-HBe seroconversion was observed in 12% and HBV resistance occurred in 13% of viraemic patients.

Resistance to FTC occurs through the same mutation points in the HBV polymerase gene as lamivudine, thus FTC is ineffective in the treatment of patients with lamivudine resistance. Since lamivudine resistance occurs in the majority of HIV/HBV coinfected patients with prolonged exposure, FTC is likely to be used in HIV/HBV patients who are naïve to therapy, or as a switch from lamivudine in patients with HBV DNA suppression. This may be a particularly attractive option given the recent FDA approval of the one pill FTC/TDF/efavirenz combination.

As with all anti-HBV therapy, abrupt withdrawals in treatment can precipitate hepatic flares. In an analysis of 251 patients across three randomized trials in chronic hepatitis B monoinfection, the incidence of hepatic flare was 7–23% with a median time to onset of 11 weeks [32*]. Posttreatment hepatic decompensation was significantly associated with bridging fibrosis and cirrhosis and one patient required liver transplantation. This issue is of particular concern in HIV-coinfected patients who may switch antiviral drugs for reasons related to HIV control. Abrupt withdrawal of any drug with anti-HBV activity should be avoided, particularly in those with limited hepatic reserve.

**Entecavir**

Entecavir, a highly potent inhibitor of HBV, has recently been approved for the treatment of hepatitis B. Two large 48-week studies comparing entecavir with lamivudine in treatment naïve HBV monoinfected patients with either HBsAg positive (n = 715) or HBeAg negative disease (n = 648) confirmed the superiority of entecavir on the study endpoints of HBV DNA suppression, alanine aminotransferase (ALT) normalization and histological improvement, although serological outcomes were similar [33**,34]. No entecavir resistance was documented, although a small percentage of entecavir-treated patients in both studies (2%) experienced virological rebound.

Entecavir is also active in lamivudine-resistant individuals, with a recent study confirming that in patients switching to entecavir, as opposed to lamivudine continuation, the two primary endpoints of histological improvement and HBV DNA suppression combined with ALT normalization were significantly more likely in the entecavir group [35**]. Although less than 2% of patients...
in this study experienced viral rebound by week 48, this was associated with genotypic mutations conferring entecavir resistance. Similar mutations were also found in 6% of patients at baseline.

An ongoing trial of entecavir in HIV/HBV coinfected has only been reported to date in abstract form [36]. Although these preliminary results suggest that entecavir is likely to be equally active against HBV in individuals with HIV coinfeciton, high rates of lamivudine resistance in this population may limit its long-term use in many. Still, entecavir will be a valuable addition for treatment in HIV/HBV individuals, particularly in treatment naïve patients who require HBV therapy but not HAART.

**Pegylated interferon**
The use of interferon to treat individuals with HIV/HBV coinfeciton has previously been associated with low rates of therapeutic success and high toxicity [37], consequently it has generally been avoided for use as a therapeutic option in coinfected patients. Several large international trials of pegylated interferon (PEGIFN), with or without lamivudine, for the treatment of both HBeAg positive and HBeAg negative HBV monoinfection, have recently rekindled interest in the use of interferon-based therapies for HBV [38–40]. At 6 months after completion of 48 weeks of therapy, rates of HBeAg seroconversion, HBV DNA suppression, and ALT normalization have all been shown to be significantly better with PEGIFN than lamivudine alone. No benefit was seen at 72 weeks for the use of PEGIFN plus lamivudine over PEGIFN alone, although HBV DNA suppression on therapy was significantly better in the combination arm. This may be of relevance in the HIV/HBV coinfection setting in which long-term nucleoside analogue therapy may be required for HIV control.

As yet there are no data on the efficacy and tolerability of PEGIFN in HIV/HBV coinfection but encouraging results from the monoinfection population, coupled with greater physician experience, suggest that in a select group of patients (CD4 count > 350 cells/mm³, no cirrhosis and elevated ALT) this therapy may have a role and future studies are awaited.

**Management of end stage liver disease in HIV and hepatitis B coinfection**
HIV/HBV cirrhotic individuals are at high risk of hepatic decompensation and hepatoma. Sudden deterioration may occur following the development of lamivudine resistance, or after the abrupt cessation of antiviral drugs. Similarly, hepatic flare due to immune reconstitution after HAART initiation can significantly worsen hepatic function in cirrhotic individuals, and may be fatal [41].

A retrospective cohort study from the United States [42*] examined the outcome of HBV coinfected patients referred for transplant assessment between 2000 and 2002. Of 35 referred patients, only nine (26%) were eligible for transplant. Of these nine, four patients were transplanted with a patient and graft survival of 100%, despite lamivudine resistance in 75%. Reasons for ineligibility were referrals both too early and too late for transplant, highlighting the need for education around transplant criteria amongst referring physicians. In this cohort with widespread lamivudine resistance (67% overall), the use of adefovir or tenofovir was the only significant differentiating factor between survivors and nonsurvivors. The benefits of adefovir and tenofovir in preventing progression of end stage liver disease have similarly been described elsewhere [43,44].

**Strategies for the therapeutic management of HIV and hepatitis B coinfection**
Advances in the understanding and management of HBV infection have recently been made but uncertainties remain. This is particularly true in coinfected individuals in whom the natural history of the disease is altered and when drugs may have dual activity against both HIV and HBV. Several guidelines have recently been published to aid clinicians in managing this complex problem with suggested algorithms for patient assessment and treatment [45**,46,47*]. Central to these guidelines is the need for adequate initial assessment of both HIV and HBV disease status, focusing on the individuals’ need for treatment of HIV, HBV or both. Significant immunosuppression should be avoided and in many patients therapy will involve dual anti-HIV and anti-HBV activity.

For those individuals who do not require HIV therapy the availability of entecavir or PEGIFN enables the treatment of HBV whilst sparing anti-HIV therapies. Low-dose adefovir is also an option in this situation but has no advantage over the use of entecavir, is less potent and carries a theoretical, although unproven, risk of HIV cross-resistance to tenofovir. New compounds such as telbivudine or clevudine, which have no anti-HIV activity, have recently demonstrated significant anti-HBV potency in phase 3 clinical trials [48–50], and may also be available for use in the future.

For individuals requiring HAART and naïve to anti-HBV therapy, combination TDF/lamivudine or TDF/FTC within HAART is recommended to maximize potency and minimize the risk of HBV resistance development. If patients are unable to tolerate HAART initiation because of immune-mediated hepatic flare, suppression of HBV DNA with entecavir for an induction period prior to antiretroviral commenecement may be a useful, although currently unproven, strategy. In HIV/HBV patients currently on lamivudine-containing HAART the presence of
HBV viraemia should be determined. If detected, lamivudine resistance is likely to be present, and in this situation other anti-HBV active drugs should be considered, particularly in the setting of cirrhosis, when suppression of HBV viraemia and prevention of hepatic flare are paramount. In most cases the most attractive option would be tenofovir, although entecavir or adefovir are also possible. Emtricitabine is not an option. There are no data on whether lamivudine should be continued or switched, although theoretically lamivudine continuation may limit resistance development, and these decisions should be considered on an individual basis. In all HIV/HBV coinfected individuals regular monitoring of HBV viraemia should occur, as should assessment for the complications of cirrhosis and HCC development.

**Conclusion**

Recent years have provided clinicians with increasing options for HBV therapy in HIV/HBV coinfected individuals, including the introduction of entecavir, emtricitabine and pegylated interferon, in addition to tenofovir, adefovir and lamivudine. The availability of these new drugs is timely given the confirmed rates of liver disease progression in the HIV/HBV coinfected population. Still, many challenges remain, including how best to combine these drugs to maximize efficacy and minimize long-term toxicity and drug resistance. The further development of therapeutic strategies to aid clinicians involved in the care of individuals with HIV and hepatitis B infection will be of benefit.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 88–90).

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8. Filippini P, Coppola N, Pisapia R, et al. Impact of occult hepatitis B virus infection in HIV patients naive for antiretroviral therapy. AIDS 2006; 20:1253–1260. This study suggests a relationship between the presence of occult HBV and hepatic flare after HAART initiation. The clinical significance of occult hepatitis B infection is currently unknown and this study adds new data to an area of clinical uncertainty.

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This paper provides 3-year follow-up data on 29 of 36 HIV/HBV patients treated with adefovir, demonstrating continued virological decline to 144 weeks, although there was a lack of virological suppression in the majority of patients. The lack of adefovir resistance raises some interesting questions and these are well addressed by an excellent accompanying editorial.


Large noninferiority study confirming the potency and tolerability of the combination tenofovir/emtricitabine with efavirenz versus zidovudine, lamivudine, efavirenz in the treatment of HIV infection.


Epidemiology of antiretroviral drug resistance in drug-naive persons
Anna Maria Geretti

Purpose of review
An update is given on the epidemiology of transmitted antiretroviral drug resistance among HIV-1-infected adults.

Recent findings
Reported prevalence surveys show inter-region and intra-region variability, in part as a result of methodological differences. Temporal trends are difficult to define as rates appear stable or declining in some cohorts but increasing in others. While the highest prevalence continues to be observed in North America, Western Europe and areas of South America, transmitted antiretroviral drug resistance is emerging in countries where access to therapy is being scaled up, including regions of sub-Saharan Africa. Resistance patterns in drug-experienced and drug-naive persons, transmission efficiency of resistant variants and their ability to persist as dominant species in the absence of drug pressure determine the prevalence of resistance mutations in persons with transmitted antiretroviral drug resistance. The most frequently detected mutations are in reverse transcriptase, especially thymidine analogue mutations, whereas protease mutations other than natural polymorphisms are generally less prevalent.

Summary
A consensus is required internationally on how transmitted antiretroviral drug resistance should be investigated and reported. Although routine testing methods provide only minimal estimates of the prevalence of transmitted antiretroviral drug resistance, successful treatment outcomes are observed in patients with resistance receiving first-line therapy guided by baseline resistance testing.

Keywords
drug susceptibility, epidemiology, fitness, resistance, transmission

Abbreviations
CRF circulating recombinant form
HAART highly active antiretroviral therapy
MSM men who have sex with men
NNRTI non-nucleoside reverse transcriptase inhibitor
NRTI nucleoside and nucleotide reverse transcriptase inhibitor
TAM thymidine analogue mutation
TDR transmitted drug resistance

Introduction
Mutations in the HIV-1 genome conferring resistance to antiretroviral drugs have been detected in plasma and cellular reservoirs of antiretroviral drug-naive HIV-1 infected patients worldwide. Several of these are recognized markers of primary or transmitted drug resistance (TDR). Others have a more uncertain classification, including some that occur as natural polymorphisms with unknown effects on drug susceptibility. There is no consensus internationally on which mutations should be regarded as markers of TDR, leading to significant discrepancies in reported surveys. There are also important differences in the composition of study cohorts. A few studies have reported population-based surveys. The majority either rely on ‘opportunistic’ samples or use resistance test results produced for routine clinical care, introducing a possible selection bias in favour of patients with the highest risk of TDR, and the potential for error due to inaccurate reporting or recording of previous antiretroviral use. Time of testing in relation to the time of infection and sensitivity of resistance testing methods are other important determinants of the likelihood of detecting TDR, as resistant mutants over time may disappear from the dominant quasispecies and become undetectable by standard methods.

Interpretation of resistance data
A recognized confounding factor in the evaluation of TDR is the method used for classifying resistance. Interpretation of sequence data is increasingly difficult given the high degree of polymorphism of circulating HIV-1 strains and the growing number of mutations found to play an accessory role in drug resistance. An ideal classification would differentiate mutations that are markers of TDR, mutations that occur as polymorphisms and either act as ‘sentinel’ markers for the presence of major resistance mutations or have a direct impact on drug susceptibility, and mutations that occur as natural
polymorphisms and have no significant effect on drug susceptibility. Automated analyses to identify sequence polymorphisms that predict resistance mutations are currently being developed. Meanwhile, the assignment of several mutations remains uncertain.

Published studies on TDR often score mutations listed by the International AIDS Society (IAS)-USA. The list is not an algorithm for assessing TDR and includes mutations that are not necessarily markers of TDR, although they may contribute to resistance in treatment-experienced patients. The approach is not uniform across published studies. In the reverse transcriptase, for example, some investigators exclude the V118I mutation as this is a polymorphism that in isolation has no significant effects on drug susceptibility. Conversely, revertants of T215YF (T215rev, T215SCDENL) are often included, as they are associated with reduced virological responses to thymidine analogues despite showing few resistance effects in vitro. In the protease, M46I/L is frequently scored as TDR as it has recognized effects on susceptibility to the protease inhibitors, although the mutation probably can occur as a polymorphism. Conversely, L33F is generally not scored as TDR as it can occur as a polymorphism, despite significant effects on protease inhibitor susceptibility [1].

Another approach to the evaluation of TDR is the use of interpretation systems, such as the Stanford Genotype Resistance Interpretation, that predict the overall levels of resistance associated with certain mutation patterns. Classification of TDR in terms of resistance levels can be misleading however, as it implies that low-level TDR has a lower potential impact than intermediate-level to high-level TDR. In fact, even mutations that do not directly confer phenotypic resistance can reduce virological responses, as seen with T215rev, by either acting as ‘sentinel’ markers for the presence of more substantial resistance within minority species in plasma or proviral DNA in cellular reservoirs, or by reducing the genetic barrier to the evolution of resistance.

Genotypic resistance assays based on automated population sequencing of plasma HIV-1 RNA offer the most effective strategy for monitoring TDR as they are widely available and relatively inexpensive, and can detect any substitution in the sequenced genes, including ‘sentinel’ mutations that do not have direct effects on the virus phenotype. Current genotypic assays, however, only detect mutants in plasma that are dominant within the quasispecies, with a prevalence of at least 15–30%. More sensitive methods for resistance testing, including the use of peripheral blood mononuclear cells (PBMC), allele-specific polymerase chain reaction, clonal analysis and single genome sequencing, can detect resistant mutants in persons lacking evidence of resistance by conventional assays. While the clinical relevance of minority and archived resistant species remains to be fully clarified, it should be acknowledged that standard tests provide only minimal estimates of TDR.

**Prevalence of transmitted drug resistance**

With the above limitations in mind, the highest prevalence of TDR has been observed in North America, Western Europe and parts of South America (Tables 1 and 2 [2,3,4,5]), reflecting the well established use of antiretroviral therapy in these regions. In New York City, resistance mutations have been detected in over 20% of homosexual males with recent infection [6**]. In Canada, the highest prevalence was also detected in white homosexual males recently infected with subtype B [7**]. Limiting the analysis to those with recent infection, however, favours the inclusion of individuals who either present symptomatically or seek regular testing [3], preventing extrapolation to the general HIV-1-infected population. When Canadian patients with established infection were included in the analysis, resistance rates were not significantly different between genders and among exposure categories and ethnic groups [7**]. In Western Europe, prevalence of TDR continues to be highest among indigenous persons [4] and those of white ethnicity infected with subtype B [5*], reflecting the imported origin of most non-B subtype infections. One important determinant of the rates of TDR in these regions is the availability of antiretroviral therapy in the countries of origin of immigrant populations. As a result, the epidemic patterns of TDR are likely to evolve over time.

In Brazil and Argentina, where antiretroviral therapy use is widely available, rates of TDR are significant, with cases reported among heterosexuals [8,9], intravenous drug users (IDUs) [10], men who have sex with men (MSM) [8] and blood donors [11**]. In Peru, a population-based surveillance conducted in six different cities investigated HIV infection and drug-resistance among MSM recruited at social venues. Resistance mutations were detected in 3.3% of HIV-1 infected persons, with the highest prevalence (5%) observed in recently infected persons in Lima [12**].

A study from Slovenia (Table 3) detected resistance mutations in 6.5% of drug-naive MSM infected with subtype B, whereas no mutations were found in other risk groups and subtypes [13*,14]. In the Republic of Georgia, where the nascent epidemic is mostly associated with IDU and heterosexual sex, antiretroviral therapy has been recently introduced with first-line regimens including lamivudine with zidovudine or stavudine plus efavirenz or nevirapine. Using PBMC to detect mutations archived within proviral DNA, 4.2% of samples collected in 1998–2003 showed the presence of the lamivudine-associated mutation M184VI [15**].
<table>
<thead>
<tr>
<th>Ref</th>
<th>Year</th>
<th>Place</th>
<th>No</th>
<th>Study group (age)</th>
<th>Risk*</th>
<th>Male</th>
<th>Subtype</th>
<th>Reported resistance</th>
<th>Mutations^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2*]</td>
<td>1997–2004</td>
<td>Italy</td>
<td>155</td>
<td>Seroconversion ≤12 months</td>
<td>MSM 24%</td>
<td>81%</td>
<td>B</td>
<td>NRTI 13.2% NNRTI 4.6%</td>
<td>RT: 41L 67N 69D 70R 74V 100I 103N 108AN 118 181CI 184IV 190AS 210W 215Y Frev 219QE PR: 48L 84V 90M</td>
</tr>
<tr>
<td>[3]</td>
<td>2000–2005</td>
<td>UK</td>
<td>140</td>
<td>Seroconversion ≤6 months</td>
<td>MSM 89%</td>
<td>Most</td>
<td>Mostly B</td>
<td>Any 6.0% ≥ 2 classes 1.4%</td>
<td>NA</td>
</tr>
<tr>
<td>[4]</td>
<td>2004–2006</td>
<td>UK</td>
<td>239</td>
<td>All new diagnoses (11–68 years) 85 seroconversion ≤125 days by avidity assay</td>
<td>MSM 53%</td>
<td>71%</td>
<td>B 56%</td>
<td>Any 7.1% NRTI 4.2% NNRTI 1.7%</td>
<td>RT: 41L 67N 103N 215rev 219Q PR: 33F 46L 48V 82AL 90M Other RT: 69DN 210F Other PR: 54T 73S</td>
</tr>
<tr>
<td>[5*]</td>
<td>2001–2003</td>
<td>Germany</td>
<td>269</td>
<td>Chronic infection, starting HAART (mean 39 years)</td>
<td>MSM 48%</td>
<td>Other 52%</td>
<td>75%</td>
<td>B 72%</td>
<td>Any 11.2% NRTI 8.6% NNRTI 3.7%</td>
</tr>
<tr>
<td>[7**]</td>
<td>2000–2001</td>
<td>Canada</td>
<td>715</td>
<td>All new diagnoses with stored sample (14–67 years) 221 seroconversion ≤170 days by STARHS</td>
<td>IDU 31%</td>
<td>80%</td>
<td>NA</td>
<td>Any 8.1% NRTI 4.1% NNRTI 1.4%</td>
<td>RT: 41L 65R 69D 70R 100I 103N 108I 1811 184IV 190A 210W 215rev 219Q 236L PR: 48L 92F 90M</td>
</tr>
</tbody>
</table>

NRTI, nucleoside and nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RT, reverse transcriptase; PR, protease; PI, protease inhibitor; NA, not available; STARHS, Standardized Testing Algorithm for Recent HIV Seroconversion.

*Risk group: MSM, men who have sex with men; Hetero, heterosexual sex; IDU, intravenous drug use.

*Mutations that may represent natural polymorphisms, have uncertain effects on drug susceptibility, or are not consistently included in TDR surveys are underlined; other mutations of interest that are described but not scored as TDR in the report are given.
Table 2 Reported prevalence of antiretroviral resistance in drug-naive HIV-1 infected persons in South America

<table>
<thead>
<tr>
<th>Ref</th>
<th>Year</th>
<th>Place</th>
<th>No</th>
<th>Study group (age)</th>
<th>Riska</th>
<th>Male</th>
<th>Subtype</th>
<th>Reported prevalence</th>
<th>Mutationsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>[8]</td>
<td>From 2004</td>
<td>Argentina</td>
<td>52</td>
<td>Seroconversion &lt;9 months</td>
<td>Hetero 52% IDU/Other 4%</td>
<td>75% BF 60% B 40%</td>
<td>Any 7.7% NRTI 1.9% NNRTI 5.9%</td>
<td>RT: 41L 103N 225H</td>
<td></td>
</tr>
<tr>
<td>[9]</td>
<td>NA</td>
<td>Porto Alegre, Brazil</td>
<td>97</td>
<td>Consecutive new diagnoses (mean 31 years)</td>
<td>Mostly Hetero 60%</td>
<td>C 58% B 32% Other: F1, mosaics</td>
<td>Any 3.1% NRTI 1.0% NNRTI 2.1%</td>
<td>RT 41L 103N 210W 215Y Other RT: 9BS 101ER 11B</td>
<td></td>
</tr>
<tr>
<td>[10]</td>
<td>1999–2001</td>
<td></td>
<td>38</td>
<td></td>
<td>NA NA</td>
<td>B 81% Other: F1, C, CRFAG, mosaics</td>
<td>Any 15.8% NRTI 13.2% PI 7.9%</td>
<td>RT: 67N 69AN 70R 11B 184V 210M 219R 219YF 219EQ PR: 30N 482A 90M</td>
<td></td>
</tr>
<tr>
<td>[11**]</td>
<td>1998–2002</td>
<td>Sao Paulo, Brazil</td>
<td>341</td>
<td>Blood donors 55 recent seroconversion by STARHS</td>
<td>NA NA</td>
<td>B 81% Other: F1, C, CRFAG, mosaics</td>
<td>Any 6.1% NRTI 4.1% NNRTI 1.2% PI 1.5% ≥ 2 classes 0.6% Recent infection: 12.7% Established infection: 5.0%</td>
<td>RT: 41L 62V 70R 75A 101N 103N 108I 151M 184V 181C 215Yrev PR: 48L 82A Other RT: 44D 67G 69ND 101R 11B 210S 238R</td>
<td></td>
</tr>
<tr>
<td>[12**]</td>
<td>2002–2003</td>
<td>Peru</td>
<td>359</td>
<td>MSM in HIV surveillance ≥ 18 years 33 seroconversion &lt;133 days by STARHS</td>
<td>MSM All B</td>
<td></td>
<td>Any 3.3% NRTI 2.2% NNRTI 1.0% PI 1.5% ≥ 2 classes 1.7% Recent infection 3.0% Established infection 3.4%</td>
<td>RT: 41L 67N 69N 74V 184V 210W 215YF PR: 30N 48L 82A 84V 90M</td>
<td></td>
</tr>
</tbody>
</table>

NRTI, nucleoside and nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RT, reverse transcriptase; PR, protease; NA, not available; PI, protease inhibitor; STARHS, Standardized Testing Algorithm for Recent HIV Seroconversion.

aRisk group: Hetero, heterosexual sex; MSM, men who have sex with men; IDU, intravenous drug use.

bMutations that may represent natural polymorphisms, have uncertain effects on drug susceptibility, or are not consistently included in TDR surveys are underlined; other mutations of interest that are described but not scored as TDR in the report are given.
The reported prevalence of TDR is low where access to antiretroviral therapy remains limited. Thus, in Kuala Lumpur, Malaysia, the prevalence of resistance mutations in recently diagnosed persons was 1% in 2003–2004, when only 22% of those in need of treatment were on highly active antiretroviral therapy (HAART) [16]. One concern is that in many resource-poor countries availability of assays for monitoring persons on antiretroviral therapy is limited and access to resistance testing nonexistent. Switching therapy based on clinical criteria means that patients will have prolonged virus replication under drug pressure, increasing the risk of drug resistance at failure and augmenting the risk of onward transmission of resistant variants. The potential impact is significant.

Rapidly spreading TDR would seriously jeopardize the effectiveness of first-line HAART, which is typically based on non-nucleoside reverse transcriptase inhibitors (NNRTIs), and therefore offers a low genetic barrier. Reassuringly, a cross-sectional survey of 398 HIV-1 infected persons who had received HAART for at least 6 months in the Chiradzulu district of Malawi showed that 84% had a plasma HIV-1 RNA load less than 400 copies/ml, indicating that implementation of large-scale simplified treatment programmes in Africa can achieve a high degree of virological success and hopefully contain the spread of antiretroviral resistance [17/18].

The appearance and evolution of TDR is one indicator of the effectiveness of efforts at preventing HIV transmission in most countries, including surveillance for transmission of resistant strains [19]. Worldwide, WHO has developed a global strategy for monitoring antiretroviral resistance in developing countries, including surveillance for transmission of resistant strains and the development of WHO guidelines for national treatment strategies [20]. Monitoring TDR is particularly important in sub-Saharan Africa, where HIV-1 transmission is widespread and access to treatment is limited. While the effectiveness of HAART against HIV-1 in some settings is encouraging, the possible impact of TDR on the population is difficult to assess, and the need for surveillance is urgent.

### Table 3: Reported prevalence of antiretroviral resistance in drug-naive HIV-1 infected persons in Eastern Europe and Asia

<table>
<thead>
<tr>
<th>Ref</th>
<th>Year</th>
<th>Place</th>
<th>No</th>
<th>Study group (age)</th>
<th>Risk a</th>
<th>Males</th>
<th>Subtype</th>
<th>Reported prevalence</th>
<th>Mutations b</th>
</tr>
</thead>
<tbody>
<tr>
<td>[13*]</td>
<td>2000–2004</td>
<td>Slovenia</td>
<td>77</td>
<td>87% of all new diagnoses (mean 36 years) 13 recent seroconversion</td>
<td>MSM 62% Hetero 30% MTC 4% IDU 3% NA 1%</td>
<td>86%</td>
<td>B 95%</td>
<td>NRTI 3.9%</td>
<td>RT: 184V 215D Other RT: 82V 69A 179D</td>
</tr>
<tr>
<td>[14]</td>
<td>NA</td>
<td>Romania</td>
<td>29</td>
<td>Drug naive (≥14 years)</td>
<td>BP/PAR 52% Hetero 48%</td>
<td>NA</td>
<td>F1</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>[15**]</td>
<td>1998–2003</td>
<td>Republic of Georgia</td>
<td>48</td>
<td>Drug-naive (mean 26 years) Proviral DNA tested</td>
<td>IDU 65% Hetero 29% BP/PAR 4% MTC 2%</td>
<td>69%</td>
<td>A 70% B 28%</td>
<td>NRTI 4.2%</td>
<td>RT: 184V</td>
</tr>
<tr>
<td>[16]</td>
<td>2003–2004</td>
<td>Malaysia</td>
<td>100</td>
<td>Drug naive, 70% diagnosed &lt;12 months (0–67 years)</td>
<td>Hetero 57% NA 43%</td>
<td>81%</td>
<td>CRFAE 64% B 12% Other: C, mosaics</td>
<td>NNRTI 1%</td>
<td>RT: 181C Other RT: 108I 118I Other PR: 33F</td>
</tr>
</tbody>
</table>

NRTI, nucleoside and nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RT, reverse transcriptase; PR, protease.

a) Risk group: MSM, men who have sex with men; Hetero, heterosexual sex; MTC, mother to child transmission; IDU, intravenous drug use; NA, not available; BP/PAR, blood, blood products or other parenteral exposure.

b) Mutations that may represent natural polymorphisms, have uncertain effects on drug susceptibility, or are not consistently included in TDR surveys are underlined; other mutations of interest that are described but not scored as TDR in the report are given.
Table 4 Reported prevalence of antiretroviral resistance in drug-naive HIV-1 infected persons in sub-Saharan Africa

<table>
<thead>
<tr>
<th>Ref</th>
<th>Year</th>
<th>Place</th>
<th>No</th>
<th>Study group (age)</th>
<th>Risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Males</th>
<th>Subtype</th>
<th>Reported prevalence</th>
<th>Mutations&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>[19]</td>
<td>2001–2004</td>
<td>Yaounde, Cameroon</td>
<td>96</td>
<td>Pregnant women diagnosed &lt;12 months</td>
<td>NA</td>
<td>0%</td>
<td>CRFAG &lt;58%</td>
<td>Any 2.1% NRTI 1.0% PI 1.0%</td>
<td>RT: 210W 215S PR: 86S</td>
</tr>
<tr>
<td>[20&lt;sup&gt;*&lt;/sup&gt;]</td>
<td>2001–2002</td>
<td>Yaounde, Cameroon</td>
<td>102</td>
<td>Recently diagnosed blood donors and hospital attendees (median 35 years)</td>
<td>NA</td>
<td>32%</td>
<td>CRFAG 59% Other: multiple</td>
<td>Any 7.8% NRTI 2.9% NNRTI 2.0% PI 2.9%</td>
<td>RT: 62V 69N 108I 184V 236L PR: 33F 46I</td>
</tr>
<tr>
<td>[21&lt;sup&gt;*&lt;/sup&gt;]</td>
<td>2004</td>
<td>Western Cameroon</td>
<td>54</td>
<td>Antenatal, STD or Health Centres attendees (≥20 years) Clonal analysis of proviral DNA</td>
<td>NA</td>
<td>4.4%</td>
<td>CRFAG 93%</td>
<td>Any 14.6% NRTI 3.7% NNRTI 5.5% PI 7.4% ≥2 classes 1.8%</td>
<td>RT: 75I 100I 184V 186C PR: 46I 82A Other RT: 44D</td>
</tr>
<tr>
<td>[22&lt;sup&gt;*&lt;/sup&gt;]</td>
<td>2003</td>
<td>Burkina Faso</td>
<td>97</td>
<td>Recent diagnoses attending hospitals and treatment centers (age 19–56 years)</td>
<td>NA</td>
<td>2.4%</td>
<td>CRFAG 49% Other: A, G</td>
<td>Any 8.3% NRTI 2.1% NNRTI 4.1% PI 2.1%</td>
<td>RT: 41I 69S 106A 108I PR: 33F</td>
</tr>
<tr>
<td>[23&lt;sup&gt;**&lt;/sup&gt;]</td>
<td>2002</td>
<td>DRC</td>
<td>70</td>
<td>Subset of sentinel population representing various subtypes</td>
<td>NA</td>
<td>NA</td>
<td>Multiple</td>
<td>Any 4.3% NNRTI 1.4% PI 2.9%</td>
<td>RT: 103N PR: 46I 90M Other RT: 179D</td>
</tr>
<tr>
<td>[24&lt;sup&gt;**&lt;/sup&gt;]</td>
<td>NA</td>
<td>Nigeria</td>
<td>18</td>
<td>Drug-naive</td>
<td>NA</td>
<td>NA</td>
<td>G 78% CRFAG</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

NRTI, nucleoside and nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RT, reverse transcriptase; PR, protease; DRC, Democratic Republic of Congo.

<sup>a</sup> Risk group: NA, not available.

<sup>b</sup> Mutations that may represent natural polymorphisms, have uncertain effects on drug susceptibility, or are not consistently included in TDR survey are underlined; other mutations of interest that are described but not scored in the report are given.
Effects on drug susceptibility, or are not consistently included in TDR surveys (Fig. 1). In recently published studies, this approach excludes A62V, T69D/N/S, V75I, A98G/S, K101Q/N, V106I, V108I, V118I, V179D, Y188I, L210M in reverse transcriptase, and L33F, M46I/L, N88S in protease, improving (albeit not resolving) comparability of different studies. Using this approach, the prevalence of protease mutations that are likely to represent TDR is 0% to 1.9% in Cameroon, 0% in Burkina Faso and Nigeria, and 1.4% in the Democratic Republic of Congo. These low estimates are consistent with the very limited use of protease inhibitors in these regions. The relatively high prevalence of protease mutations detected in Western Cameroon (7.4%) is likely to reflect the more sensitive testing method, based on clonal analysis of proviral DNA [21]. Several of the mutations were found only in some of the clones studied and the significance is uncertain in the absence of further investigation.

**Patterns of transmitted resistance**

Mutations conferring resistance to the nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) are the most common form of TDR detected worldwide (Fig. 1). NNRTI resistance is also highly prevalent and rising in some areas, in part reflecting local prescription patterns, whereas protease inhibitor resistance is generally less frequent. Although some drug-naive patients in developed countries carry multidrug-resistant virus, many have preserved treatment options. The prevalence of mutations affecting two antiretroviral drug classes ranges from 0% to 9.8%, whereas triple class resistance mutations occur in 0–2.7% of drug-naive persons.

The most common mutations reported in persons with TDR are the thymidine analogue mutations (TAMs, codons 41, 67, 70, 210, 215, 219) for the NRTIs (Fig. 2), K103N, Y181C and G190A for the NNRTIs, and V82A/F and L90M for the protease inhibitors (if codon 46 mutants are excluded) [2,4,5,6,7,8,9]. The mutational patterns described frequently involve a single mutation [2,4,5,6,7,9]. Although multiple mutations, especially TAMs, are also observed. Among drug-naive persons in the UK, Germany and Brazil, 1.3%, 3% and 1.8%, respectively, showed a single TAM, 1.3%, 1.1% and 0.9% showed two, and 0.8%, 0.7% and 0.3% showed three TAMs [4,5,10].

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**Figure 1** Conservative estimates of prevalence of transmitted drug resistance in different regions and by drug class

<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage with resistance mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK n = 154</td>
<td>Any</td>
</tr>
<tr>
<td>UK* n = 85</td>
<td>NRTI</td>
</tr>
<tr>
<td>Germany n = 269</td>
<td>NNRTI</td>
</tr>
<tr>
<td>Argentina n = 52</td>
<td>PI</td>
</tr>
<tr>
<td>Brazil, Porto Alegre n = 97</td>
<td>&gt;1 class</td>
</tr>
<tr>
<td>Brazil, Rio n = 38</td>
<td></td>
</tr>
<tr>
<td>Brazil, S. Paulo n = 280</td>
<td></td>
</tr>
<tr>
<td>Brazil, S. Paulo* n = 55</td>
<td></td>
</tr>
<tr>
<td>Slovenia n = 77</td>
<td></td>
</tr>
<tr>
<td>Georgia n = 48</td>
<td></td>
</tr>
<tr>
<td>Malaysia n = 100</td>
<td></td>
</tr>
<tr>
<td>Younque, Cameroon n = 96</td>
<td></td>
</tr>
<tr>
<td>Younque, Cameroon n = 102</td>
<td></td>
</tr>
<tr>
<td>W. Cameroon n = 54</td>
<td></td>
</tr>
<tr>
<td>Burkina Faso n = 97</td>
<td></td>
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<tr>
<td>DRC n = 70</td>
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Readers should refer to Tables 1–4 for details of the study cohorts. References are in parentheses. Studies giving insufficient information on mutation patterns were excluded. Data from Rio de Janeiro, Brazil, include those for the 1999–2001 cohort only. Data from the UK and Sao Paulo, Brazil include persons with established and recent infection. DRC, Democratic Republic of Congo; NRTI, nucleoside and nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
There are multiple factors that influence the prevalence of individual resistance mutations in drug-naïve HIV-1 infected persons. If treatment-experienced persons with resistance are the main source of TDR, obvious determinants include prescribing policies, and rates of virological failure and resistance patterns in the potential transmitters. TAMs and M184V are the most common mutations currently detected in treatment-experienced patients [2/C15], reflecting the extensive use of zidovudine, stavudine and lamivudine, but also previous mono and dual NRTI therapy in the pre-HAART era and the suboptimal use of therapy in the early HAART era. A decline in the prevalence of TAMs is being observed in treatment-experienced cohorts in Western Europe, as a consequence of changing prescribing patterns, improved use of therapy and prompt management of treatment failure. TDR patterns are also likely to evolve over time, at least in resource-rich settings that are moving away from thymidine-based regimens and can adopt close monitoring and early management of virological failure.

Overall rates of resistance are higher in treatment-experienced HIV-1 infected cohorts compared with drug-naïve recently infected persons [2/C15,12/C15/C15], consistent with the view that resistant mutants have a transmission disadvantage relative to wild-type virus. The relative efficiency of transmission of resistant mutants can be estimated by comparing resistance patterns of potential transmitters with those of recently infected persons residing in the same area [2/C15], provided they are part of the same transmission networks. Several mutations are detected in treatment-experienced persons but are
uncommon in recently infected patients, suggesting a hierarchy in transmissibility. Thus, in reverse transcriptase, M184VI and T215YF may have a relative transmission disadvantage when compared with Y181CA and K219QE, while in protease, L90M may be more efficiently transmitted than D30N or G48V [6**]. Interestingly, T215rev, one of the most common forms of TDR, shows similar prevalence in treatment-experienced persons and recently infected patients, suggesting efficient transmission. Preliminary data indicate that T215rev may be responsible for the primary infection [2*], although reversion can also occur after transmission of T215YF, due to the improved fitness of T215rev relative to T215YF [24**].

**Temporal trends**

Prevalence of TDR shows conflicting trends across different cohorts, with some studies showing stable or declining prevalence whereas others show increasing rates. A survey of 361 patients with recently acquired infection in New York City found a substantial increase in the number of persons with resistance mutations, from 13.2% in 1995–1998 to 24.1% in 2003–2004, when analysing cohorts with relatively comparable demographic and clinical characteristics [6**]. Resistance increased from 11.8% to 16.1% for the NRTIs, 2.6% to 13.4% for the NNRTIs and 1.3% to 7.1% for the protease inhibitors. The prevalence of resistance to two or more drug classes also rose from 2.6% to 9.8%. A population-based survey conducted among newly diagnosed persons in Canada similarly found that prevalence increased from 6.1% in 2000 to 10.1% in 2001, whereas the demographic characteristics of the population stayed constant [7**].

TDR trends have multiple determinants. They may represent random fluctuations or erroneous estimations if small cohorts are analysed. Rising rates may accompany growing access to antiretroviral therapy, or earlier initiation of therapy and increased use of treatment interruptions in some cohorts, or indicate increasing high-risk behaviour in certain groups. Conversely, advances in treatment strategies, improved virological control of treated persons, prompt management of treatment failure and declining rates of resistance in drug-experienced populations will reduce the risk of TDR. HAART success is a key determinant. In Denmark, while the proportion of HIV-1-infected persons receiving therapy increased from 44% in 1997 to 82% in 2004, the occurrence of NRTI and protease inhibitor failure declined over time [5*]. Using previous treatment failure as a proxy for acquired drug resistance, the proportion of potential transmitters of resistance also declined over time, correlating with the low (5% or less) rates of TDR recorded in the same cohort. It is generally assumed that treated patients with chronic infection act as the main source of TDR. Phylogenetic analysis of virus isolates from cohorts with acute or recently acquired HIV-1 infection often detect transmission clusters with TDR [6**], however, suggesting that subjects with recent infection are an important source of resistant virus, and identifying an important self-fuelling mechanism for TDR.

**Persistence of resistant mutants and fitness considerations**

Unlike resistance mutations acquired during therapy, transmitted resistant mutants can persist long term in plasma in the absence of drug pressure and also persist within proviral DNA of persons with suppressed virus replication [26**]. One proposed scenario is that soon after infection, a narrow or homogenous viral population becomes established as the dominant quasispecies in plasma and cellular reservoirs, allowing no effective competition with wild-type virus [26**]. Back-mutation of transmitted mutants to wild-type may occur over time, although in some cases the transmitted mutants become genetically fixed by compensatory mutations and unable to revert to wild-type without a loss of fitness. Superinfection may be an alternative source of wild-type virus, and may occur even in patients with long-standing infection [27*].

Evolution of TDR does occur over time. In cohort studies, detection of TDR is predicted by a shorter time since HIV diagnosis [5*] or a higher CD4 count [4], and TDR prevalence is typically higher in recent than in established infection [7**,11**]. This is likely to reflect growth advantage of wild-type virus over resistant mutants, although differences in study populations or changes in transmission rates can also play a role. Over a median 15 months (range 10–23) of follow-up, reversion (by standard genotypic testing) to either other codons or wild-type is seen commonly with T215YF, K70R and M184V, less commonly with D67N, T215F, K219N and Y181C and uncommonly for M41L, T69DN, G190S, L210W, T215LCE and K219Q in reverse transcriptase and I84V and L90M in protease [24**]. These observations indicate that the stability of transmitted resistant mutants in the absence of drug pressure varies considerably, probably reflecting different fitness costs. The findings also contribute to explaining the mutational patterns observed in chronically infected persons with TDR. It should be noted, however, that retention of transmitted resistant mutants in proviral DNA has been documented, indicating that TDR can have long-lasting effects and that empirical antiretroviral therapy may be suboptimal [26**].

**Conclusion**

Conservative estimates indicate that prevalence of TDR is significant in countries where antiretroviral therapy is well established. Excellent immunological and virological responses are observed among patients with TDR.
started on HAART [5,6,28], especially if regimens are designed according to baseline resistance test results [5,6]. Thus, in countries with evidence of TDR, baseline resistance testing should be the standard of care for all new HIV-1 diagnoses to guide the choice of antiretroviral drugs, ensuring successful treatment outcomes and preventing onward transmission of resistant virus.

Experience to date indicates that emergence of TDR inevitably follows the introduction and increasing use of antiretroviral therapy in a population. This suggests that countries where access to therapy is currently being scaled up are becoming vulnerable to the risk of TDR. Recent data provide support to this hypothesis, as surveys from Eastern Europe, Asia, and sub-Saharan Africa have begun to report TDR in their drug-naive HIV-1-infected populations. Monitoring the prevalence of TDR in these regions provides important epidemiological information on the success of therapy in treated populations and is necessary to inform national treatment guidelines.

The variation in the local epidemiology of TDR is significant. Although multiple factors determine the risk of TDR in different regions and populations, there is an urgent need for standardized surveillance and reporting strategies. Characterization of the genetic diversity of HIV-1 strains is an important prerequisite to aid the development of appropriate guidelines for surveying TDR.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

• • of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 90–91).


The paper identifies a significant association between treatment with amprenavir and emergence of the protease mutation L33F and demonstrates that the mutation has a significant effect on phenotypic susceptibility to amprenavir, ritonavir, lopinavir and to a lesser extent saquinavir. The mutation may also be selected by atazanavir, tipranavir and darunavir, suggesting that its presence should be monitored in treatment-naive persons.


The paper identifies several resistance mutations that although common in treatment-experienced persons are uncommon in recently infected persons, suggesting that certain mutations have a greater transmission efficiency than others.


The paper provides a well described report of resistance patterns in drug-naive persons with drug-resistance and demonstrates that first-line HAART guided by baseline resistance testing has comparable efficacy in persons with and without evidence of TDR.


The paper describes high and rising rates of TDR in recent seroconverters in New York City, and demonstrates that initiation of HAART guided by baseline resistance testing achieves excellent virological and immunological responses despite evidence of TDR. The authors also identified significant clusters among persons with TDR, indicating that people who acquire TDR are an important source on onward transmission of drug-resistant virus.


The paper provides a population-based survey of TDR in Canadian persons and demonstrates that although the risk of TDR is highest in recently infected homosexual males of white ethnicity, it is not limited to this group.


The paper describes a large survey of antiretroviral drug resistance among blood donors in Brazil, where blood donation programmes preclude paid donations and exclude prospective donors who acknowledge risk factors for HIV infection. A variety of HIV-1 subtypes were identified and the reported prevalence of TDR was high, especially among persons with recent seroconversion.


The paper demonstrates that surveillance of antiretroviral resistance can be successfully linked to that of HIV infection to provide TDR estimates that can be extrapolated to the general HIV-1 infected population. The low rate of TDR detected in 2002–2003 was consistent with the low treatment rates before 2004, and provides a baseline for ongoing monitoring as access to antiretroviral therapy improves in the Peru.


The paper provides a well described survey of antiretroviral resistance in newly diagnosed persons in Slovenia, indicating that the homosexual males infected with subtype B are currently the group at the greatest risk of TDR in Slovenia.


The authors characterised HIV-1 F strains circulating in Georgia by partial pol sequencing of 48 samples and near full-length genome sequencing of five samples. Results demonstrated that the HIV-1 epidemic in the country is associated predominantly with subtype A strains also circulating in Ukraine, Russia and Uzbekistan (referred to as subtype Avo), although subtype B strains are also common. Proviral DNA analysis of the samples detected a low prevalence of TDR at a time that preceded expanded access to antiretroviral therapy.


The paper describes the outcomes from a large scale simplified HAART programme in HIV-1 infected adults in Mali. Analysis of survival indicators, CD4 count changes, virological responses and adherence levels after at least 6 months of HAART indicated excellent treatment outcomes, with infrequent treatment discontinuation and high rates of virological suppression.

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HIV infection and AIDS


The paper describes the WHO proposed simplified approach to antiretroviral therapy for developing countries scaling up access to antiretroviral therapy, on the basis that western models of specialist physician management and advanced laboratory monitoring are not feasible in resource-poor settings. The need for population-based surveillance of both acquired and transmitted drug resistance is acknowledged.


The paper provides a well described analysis of the prevalence of resistance mutations among drug-naive persons in sub-Saharan Africa, indicating that polymorphisms are common in cohorts where multiple subtypes circulate and highlighting the difficulty of reliably scoring mutations as indicative of TDR in these settings.


The paper provides a well described analysis of the prevalence of resistance mutations among drug-naive persons in sub-Saharan Africa, indicating that polymorphisms are common in cohorts where multiple subtypes circulate and highlighting the difficulty of reliably scoring mutations as indicative of TDR in these settings.


Using clonal analysis of proviral DNA, the authors demonstrate that resistance mutations can be detected in drug-naive persons in Cameroon, although the clinical relevance of the more rare mutants is uncertain.


The paper describes the highly diverse nature of HIV-1 strains circulating in DRC, where a high proportion of recombinants show complex mosaic structures. Not surprisingly, a high degree of polymorphism was detected in protease sequences.


The paper describes the high degree of polymorphism of pol sequences from HIV-1 G and CRFAG strains circulating in Nigeria, and reports good phenotypic susceptibility to the three main classes of antiretroviral drugs, with the exception of a few isolates showing slightly reduced susceptibility to ritonavir and/or nevirapine.


The authors describe the evolution of transmitted resistance mutations over time and demonstrate that stability in the absence of drug pressure varies for different mutants, probably reflecting different effects on viral fitness.


Starting from the assumption that patients on antiretroviral therapy are the main source of TDR, the authors discuss how declining rates of treatment failure among Danish HIV-1 infected patients are likely to result in a decreasing risk of transmission of drug resistant virus.


The paper demonstrates that resistance profiles of persons with TDR are identical in HIV-1 sequences detected in plasma RNA and proviral DNA soon after infection, supporting the hypothesis that infection is established with a homogenous virus population. Absence of detectable wild-type virus was consistent with this observation. Resistance mutants were found to persist long-term in proviral DNA of persons receiving HAART.


The paper demonstrates superinfection in a patient with long-lasting infection, followed by recombination between the infecting strains.


Interesting paper suggesting that TDR is associated with a more rapid CD4 decline in the first year after infection but not subsequently.
Circumcision and HIV transmission
Thomas C. Quinn\textsuperscript{a,b}

Purpose of review
To review the recent literature on male circumcision and its effect on HIV acquisition.

Recent findings
The report from the randomized clinical trial of male circumcision in South Africa demonstrating a 60% protective effect in preventing HIV acquisition provided the first clinical trial evidence of efficacy of male circumcision in protecting men against HIV infection. This protective effect was consistent with both ecological and epidemiologic studies which also show a protective effect of 50–70% in men at high risk for HIV infection. Biological studies also demonstrate an increased number of HIV receptor cells in the mucosa of foreskin providing additional evidence of HIV susceptibility in the uncircumcised male. Male circumcision may also have a beneficial effect in preventing HIV acquisition in women and lowering selected sexually transmitted infections in both sexes.

Summary
The results of two ongoing randomized clinical trials of male circumcision in Kenya and Uganda are awaited with interest, however male circumcision should be carefully considered as a potential public health tool in preventing HIV acquisition. If other trials confirm the results of the South African trial, implementation of this surgical procedure will need to be carefully scaled up and integrated into other prevention programs with emphasis on surgical training, aseptic techniques, acceptability, availability and cultural considerations.

Keywords
AIDS, circumcision, epidemiology, HIV, prevention, transmission

Introduction
Male circumcision is one of the oldest surgical procedures dating back to Egypt’s sixth dynasty (2345–2181 BC)\cite{1}. Male circumcision is the surgical removal of all or part of the prepuce (foreskin) of the penis, which is practiced as part of a religious ceremony performed shortly after birth, a traditional ‘coming of age’ ritual practiced at or after puberty in certain cultures, or as a medical procedure related to infections, injury, or anomalies of the foreskin. In some countries, such as the United States, it is considered a preventive medical procedure to reduce the frequency of urinary tract infections and phimosis in young boys and potentially to reduce the acquisition of sexually transmitted infections (STIs). Common among Muslim and Jewish men, rates of circumcision vary widely as a surgical practice among ethnic populations and by geographical location. For example, circumcision may be common (60–70%) among men in the United States, but is rare (1–5%) among men throughout Europe and Latin America. Data from the National Health and Nutrition Examination Survey (NHANES)\cite{2} on the frequency of circumcision in men in the United States between 1999 and 2002 demonstrated that the overall prevalence of circumcision was 79%, but it varied by race/ethnicity: 41% in Mexican Americans, 78% in non-Hispanic blacks, and 89% in non-Hispanic whites. Among boys born in the 1980s, the prevalence of circumcision was 83%, a significant decrease from its peak of 91% in men born in the 1970s.

Epidemiological associations
Circumcision practices also vary widely by culture and religious beliefs throughout sub-Saharan Africa and Asia. It was this noted variance in circumcision practices in sub-Saharan Africa that caused investigators to note an initial association between HIV and the lack of male circumcision in the late 1980s. These studies, referred to as ecological studies, demonstrated a definitive geographic correlation of high HIV prevalence in areas where male circumcision is rare. Ecological studies, while highly supportive of an association between HIV acquisition and lack of male circumcision, have been faulted due to confounding of behavioral factors, religion, culture, and geography. Extensive epidemiologic studies were therefore conducted to examine the relationship between the practice of circumcision and HIV incidence. More than 40 epidemiologic studies have shown a significant association between lack of male circumcision and acquisition of HIV in men\cite{3,4}. Several reviews have shown that the risk of HIV acquisition in uncircumcised heterosexual
men is 1.8–11.2 times higher than in circumcised men [5]. The protective effect appears to be strongest for higher-risk men, with a subanaylsis of 16 studies of high-risk men showing that circumcised men were 70% less likely to contract HIV (relative risk 0.3). After adjustment for likely confounders, such as marital status, age, condom use, number of sexual partners, alcohol consumption, income and education, the strength of the association of HIV with lack of circumcision increased. Among men who have sex with men studied in the US, acquisition was increased twofold among uncircumcised men compared with circumcised men, although the population attributable risk was only 10% due to the high frequency of circumcision in the US male population [6*].

In Rakai, Uganda, among male partners of HIV-positive women in regular sexual relationships, 40 of 137 (29%) uncircumcised men and none of 50 (0%) circumcised men seroconverted over a 4-year period (P < 0.001) [7]. A similar association between circumcision and lack of seroconversion was found among Nairobi men attending STI clinics after a history of sex with seropositive commercial sex workers [8]. In India HIV prevalence was found to be seven times higher among uncircumcised men and was independent of acquisition of other STIs [9]. A 2004 population-based Kenya demographic and health survey found a fourfold higher HIV prevalence among uncircumcised men than circumcised men [10*,11,12].

In a recent study in Rakai, Uganda the effects of male circumcision on HIV and STD acquisition were examined in their female partners [13]. The incidence of female HIV acquisition was 6.6 per 100 person-years in wives of circumcised HIV-positive men compared with 10.3 per 100 person-years in wives of HIV-positive uncircumcised men. The risk of STDs in the female partners of circumcised versus uncircumcised men was also significantly reduced for trichomonas and bacterial vaginosis but not for chlamydia and gonorrhea. The sample size was too small to effectively examine the effect of decreasing acquisition of herpes simplex virus (HSV) or human papillomavirus. The risk for female genital ulcer disease was also reduced in wives of circumcised men but this was confounded due to the low prevalence and incidence of HIV in these wives.

Turner and coworkers [14] also addressed the role of men’s circumcision status and women’s risk for HIV in Zimbabwean and Ugandan women. Among 4448 women, 23.2% reported at baseline that their primary partner was circumcised. The hazard ratio for HIV acquisition comparing women whose primary partner was circumcised with women whose primary partner was uncircumcised was 0.75 (95% confidence interval (CI) 0.53–1.06). Following multivariate adjustment for country, recruitment population, age, and hormonal contraceptive use, the hazard ratio was attenuated. The study investigators concluded that crude analyses suggested that women partnered with circumcised men may be at lower HIV risk, but the association was weakened with adjustment for other risk factors, particularly age and recruitment population.

In a study by Drain and colleagues [15], the relationship between male circumcision prevalence, religion, and seven infectious diseases was evaluated using country-specific data among 118 developing countries. In their analysis, male circumcision was associated with lower HIV prevalence and lower cervical cancer incidence but not with reductions in HSV-2, syphilis, nor, as expected, hepatitis C, tuberculosis, or malaria. In multivariate analysis controlling for religion, circumcision was significantly associated with lower cervical cancer incidence and lower HIV prevalence independent of Muslim and Christian religion. Male circumcision was also strongly associated with lower HIV prevalence among countries with primarily sexual HIV transmission, but not among countries with primarily injecting drug user (IDU) transmission. These findings strengthen the reported biological link between male circumcision and STIs, including HIV and cervical cancer [16*,17,18].

**Randomized clinical trials**

Three randomized controlled trials were initiated to assess the safety and efficacy of male circumcision in reducing female-to-male HIV transmission in Kenya, Uganda, and South Africa. In Uganda, a randomized controlled trial of male circumcision of HIV-positive men is underway in order to examine the effect of male-to-female HIV transmission. The South African study in Orange Farm [19*] was stopped prematurely in mid-April 2005 on the recommendation of the study’s Data Safety Monitoring Board (DSMB) and the male circumcision intervention was offered to the control group. Trial data were analyzed and demonstrated a 60% protective effect (95% CI 40–80%) for adult male circumcision. In that study a total of 3274 uncircumcised men, aged 18–24 years, were randomized to a control group or an intervention group with follow-up visits at 3, 12, and 21 months. Male circumcision was offered to the intervention group immediately after randomization and to the control group at the end of the follow-up. The mean follow-up period was 18.1 months when the study was stopped prematurely by the DSMB. There were 20 HIV infections (incident rate = 0.85 per 100 person-years) in the intervention group and 49 (2.1 per 100 person-years) in the control group, corresponding to a rate ratio of 0.40 (95% CI 0.24–0.68%; P < 0.001). This rate ratio corresponds to a protection of 60%. When controlling for behavioral factors including sexual behavior, which
increased slightly in the intervention group, condom use and health-seeking behavior protection, the protective effect was 61% (95% CI 34–77%).

This study provided the first experimental evidence of the efficacy of male circumcision in protecting men against HIV infection [20,21]. The demonstration in this study of a causal association between HIV infection and male circumcision is consistent with protection suggested by metaanalysis of the observational studies but with a higher protective effect. A major limitation of this study is that participants were followed for only a short period of time due to the cessation of the study by the DSMB. Consequently, this study does not explore the long-term protective effect of male circumcision. Nevertheless, at least for the general population in South Africa where this study took place, the trial clearly documents the protective effect of circumcision, providing an efficacy rate analogous to what could be hopefully expected from a vaccine trial. The study does not directly address the impact of male circumcision on male-to-female HIV transmission nor were the investigators able to provide data on the effects on other STIs.

Since this study was limited to only one population in South Africa, the World Health Organization (WHO) and the United Nations Joint Programme on HIV/AIDS (UNAIDS) have recommended that planning for male circumcision in other areas including acceptability, feasibility, and training be initiated while awaiting the outcomes of the remaining two randomized control trials. The two further randomized controlled trials ongoing in the Rakai region of Uganda and the Kisumu region of Kenya will hopefully provide additional information regarding the efficacy of circumcision as a preventive procedure [22]. The Ugandan trial is in a rural setting and involves 5000 participants aged 15–49 years. The Kenyan trial involves 2784 men aged 18–24 years in an urban setting. The two trials are due to be completed in 2007 and an interim review of the data was conducted in June 2006 with continuation of the study with a planned analysis in December 2006.

**Biological causality**

Biological explanations for decreased susceptibility to HIV in circumcised men include the ability of the internal foreskin to absorb HIV more efficiently due to the greater presence of Langerhans cells and other HIV target cells, and the greater susceptibility of the foreskin in the uncircumcised men to tears, abrasions, and infections by STIs and subsequently HIV. Circumcision may also result in increased keratinization of the glands when not protected by the foreskin, resulting in a short drying period after sexual contact, reducing the life expectancy of HIV on the penis after sexual contact with an HIV-positive partner and reduction of total surface of the skin of the penis and reduction of target cells which are numerous in the foreskin. The finding of an increased frequency of Langerhans cells and macrophages present near the surface of the epithelium of the inner foreskin where there is no or minimal keratin barrier suggests a strong biological effect in susceptibility to HIV in uncircumcised men. Thus, it is plausible that circumcision reduces the risk of HIV acquisition through the penis by physically removing HIV-1 target cells positioned close to the mucosal surface of the inner foreskin. Primary infection is most likely to occur when there is little or no overlying protective layer of keratin, whereas in contrast in a circumcised man, keratinized epithelium covers the entire surface of the penis.

The results from Patterson et al. [23] suggest that men with a history of STIs have a higher density of HIV target cells on the inner mucosal surface of their foreskin than men with no STI history. Donoval et al. [24] also quantified HIV-1 target cells in foreskin tissue obtained from men aged 18–24 years who were undergoing circumcision in Kisumu, Kenya. Unlike Patterson et al. [23], they did not find any differences in CD4+ cells between men with or without a history of STIs. Langerhans cells and macrophages, however, were more abundant in the group with a history of infection. The densities and positions of HIV target cells in the foreskin tissue of these Kenyan men indicate that the inner mucosal surface of the human foreskin contains cells that make it highly susceptible to HIV infection. An elegant study by McCoombbe and Short [25] demonstrated that both the inner aspect of the foreskin and the frenulum are poorly keratinized and are richly supplied with HIV-susceptible cells. Of the cells tested, Langerhans cells are the most likely to be encountered as they are most superficial and have dendritic processes sampling a large epithelial surface area.

An alternative hypothesis for protection in circumcised men was suggested recently by Wawer et al. [26] in Rakai, Uganda. In a metaanalysis, Wawer et al. found HIV acquisition in circumcised compared with uncircumcised men was 0.29 (95% CI 0.20–0.41) in men with high-risk behaviors compared with an adjusted relative risk of 0.56 (95% CI 0.44–0.70) in the general male population. One hypothesis for why circumcision is more protective in high-risk men is because the procedure may reduce the risk of genital ulcer disease, a cofactor for HIV acquisition. Wawer et al. [26] also suggested that the urethral meatus represents a small area of vulnerable mucosa and in circumcised men experiencing recurrent exposure to low-dose HIV, antigenic stimulation by repeat subinfectious inoculums may induce a mucosal immune response enhancing protection over and above the reduced risk afforded by removal of the foreskin per se. The induction of this mucosal immunity has been observed in highly
exposed but uninfected members of HIV-discordant couples and in commercial sex workers among whom there were enhanced mucosal CD8 T-cell responses and HIV-1-specific immunoglobulin A [27,28]. Thus, circumcision may protect men by three possible mechanisms: an anatomical mechanism consequent on the removal of all vulnerable foreskin mucosa; the reduction of cofactors such as genital ulcer disease; and the induction of a mucosal immune response in the presence of repeated antigen stimulation [26*].

Acceptability

Twelve published studies and two unpublished manuscripts found reasonable acceptability of circumcision in Botswana, Kenya, Malawi, South Africa, Swaziland, Tanzania, Uganda, Zambia, and Zimbabwe ranging from 29 to 80% (mean 60%) [29,30*,31]. Men were asked whether they would choose circumcision for themselves and their sons and women were asked about acceptability for their husbands and sons. In Botswana, a 1 h information session increased acceptance rates from 60 to 80%. In Malawi 32 focus group discussions were conducted with 159 men and 159 women aged 16–80 years. Acceptability was lowest in the north where the practice was little known, higher in younger participants, and higher in central and southern districts where male circumcision is practiced by a minority Muslim group. Barriers to circumcision include fear of infection and bleeding, cost, and pain. Facilitators include hygiene, reduced risk of STI, religion, medical conditions, and enhanced sexual pleasure. If male circumcision services are introduced in Malawi, acceptance is likely to vary by region but many parents and young men would use the services if they were safe, affordable, and confidential. These studies in which most of the uncircumcised African men express interest in becoming circumcised if performed safely and affordably highlighted the potential of the procedure as a population-level intervention to reduce HIV spread. Nevertheless, cultural practices may persist as barriers to male circumcision in certain selected areas such as in India and Asia, where the procedure is rarely practiced.

Safety and complications

Complications of circumcision include excessive bleeding, infection, excessive pain, too much skin removed, anesthetic complications, penile damage or amputation, cosmetic complications, erectile dysfunction, psycho-behavioral complications, HIV infection from nonsterilized instruments and possibly death if appropriate treatment of complications is not provided [32]. It should be noted from most studies, however, that serious complications are rare. Complications have been reported by fewer than 4% of the participants in the South African, Kenyan, and Ugandan trials, and none of the complications were life-threatening or serious. However, it is likely that complications could increase if circumcision is scaled up and performed in areas under nonsterile conditions or by practitioners with little experience [33*]. In Zambia 16% of men are circumcised and HIV prevalence overall is 16% [34]. According to their survey, meeting the existing demand for circumcision services is hampered by a shortage of skilled providers; lack of dedicated space for health education, counseling, and surgery in existing health facilities; shortage of supplies; high cost, especially in the private sector; and the fact that this ‘elective’ procedure is given low priority by healthcare providers [35]. Recommendations have been made for circumcision services to be prioritized and made part of a package that includes male reproductive health services.

Due to the potential complications and the uncertainty of benefit to a low-risk population, scaling up circumcision as a preventive measure worldwide has met with some controversy [36,37*,38,39*]. Fox and Thomson [40] argue strongly that it is ethically inappropriate to subject children whether male or female to the acknowledged risk of circumcision and contend that there is no compelling legal authority for the common view that male circumcision is lawful. They criticize the continued professional willingness to tolerate the nontherapeutic, nonconsensual excision of healthy tissue, arguing that in this context both professional guidance and law are uncharacteristically tolerant of risk inflicted on young children given the absence of clear medical benefits. Although published after the results of the trial of the South African circumcision trial, the authors fail to address the scientific evidence supporting the public health effect of circumcision. Instead, they quote Benatar and Benatar’s [41] conclusion following a review of the literature that none of the scientific evidence ‘is anywhere near conclusive’. It is likely that papers such as this and others [42] will continue until the results of the other two trials are completed and the effect of circumcision is documented in populations other than the completed trial on South Africa.

Circumcision as an HIV prevention intervention

Mathematical models of implementing male circumcision in countries with high incidence rates also suggest marked reductions in HIV infection in men with subsequent decreased transmission rates to women in a cost-effective manner [43**]. Moses and colleagues [44] presented two mathematical models regarding the public health impact of male circumcision on HIV prevention. With varying assumptions ranging from 50 to 80% uptake of circumcision in a population in which 90% of men were uncircumcised, the introduction of male circumcision resulted in large and sustained declines in HIV prevalence over time among both men and women. In a random mixing model, decreases in HIV prevalence of up
to 60% among men and 30% among women were calculated. The authors concluded that large-scale uptake of circumcision services in African countries where circumcision is rarely practiced and HIV prevalence is high could lead to a substantial reduction in HIV prevalence over time in both men and women. Lloyd-Smith and coworkers [45] also used mathematical models to measure the potential impact of circumcision on the AIDS epidemic in Africa. In summary, they found that increased circumcision coverage could avert 2.0 million new HIV infections and 0.3 million deaths in the period 2005–2015 in sub-Saharan Africa. In the following 10 years it could avert a further 3.7 million new infections and 2.7 million deaths, with one quarter of all incident cases prevented and deaths averted occurring in the country of South Africa. Full circumcision coverage is predicted to increase the proportion of infected people that are women from about 52% to about 58%. Using a conservative estimate, circumcision is equivalent to an intervention such as a vaccine or increased condom use that would reduce transmission from male to female and female to male by 37%. Thus, while the protection of HIV-negative people would be immediate, the full impact of circumcision on HIV-related illness and death would not be felt for 10–20 years.

Kahn and coinvestigators [46] conducted a cost-effectiveness model based on the completed South African circumcision trial. At full male circumcision coverage, each 1000 circumcisions would avert an estimated 308 infections over 20 years, two-thirds in men and one-third in women. The cost is US$181 per HIV infection averted, with net savings of US$2.4 million. Cost-effectiveness is sensitive to the cost of male circumcision and if averted HIV treatment, the protective effect of circumcision, and HIV prevalence. With HIV prevalence of 8.4%, the cost per HIV infection averted is US$550 and net saving is US$753,000. In settings in sub-Saharan Africa with higher HIV prevalence among the general population, adult male circumcision appears to be cost-effective when adjusted for averted HIV medical cost savings.

Conclusion

Research over the past 20 years has demonstrated a strong association between HIV infection and the lack of male circumcision in sub-Saharan Africa, Asia, and the United States. The completion of one randomized clinical trial of male circumcision demonstrated a 61% protective effect against HIV acquisition in South Africa, necessitating the early termination of the trial and offering circumcision to the control arm. Two additional randomized controlled trials in Uganda and in Kenya are still underway and recommendations regarding the integration of male circumcision as a preventive measure have been postponed pending the results of the remaining trials. If these two trials result in a significant protective effect due to circumcision, it is likely that widespread male circumcision could lead to a strong reduction in the spread of HIV in high incidence areas such as sub-Saharan Africa. There are concerns that still need to be addressed, however, such as the change in sexual behavior, surgical complications such as infection and bleeding and acceptance of a surgical procedure for prevention of HIV. Consequently, if male circumcision is to be introduced widely pending the results of the two remaining trials, it will be crucial to design programs that provide a balance between promotion of male circumcision as an HIV prevention tool and providing all individuals with the full spectrum of other HIV prevention practices.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 90).


This Cochrane systematic review assessed the evidence of male circumcision in reducing HIV risk in men through heterosexual intercourse. The authors concluded that while most studies show an association between circumcision and prevention of HIV, the results may be limited by confounding factors such as religion and cultural practices.

4 Wilson D, de Beyer J. Male circumcision: evidence and implications. HIV/AIDS M&E. ‘Getting Results’ series; October 2006. World Bank Global HIV/AIDS Program. An excellent review article that summarizes the ecological, epidemiological, and biological evidence associating lack of circumcision with increased risk for HIV. The paper also describes the Auvert et al. randomized controlled trial of circumcision [19**] and its policy implications.


One of the few papers that demonstrate that lack of circumcision increases HIV risk among men who have sex with men.

7 Quinn TC. Circumcision and HIV transmission: the cutting edge. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; 5–8 February 2006; Denver, Colorado. Abstract 120.


This paper suggests that differences in biological factors such as circumcision in sexually transmitted infections may be equally or more important in assessing risk for HIV than differences in sexual behavior.

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This first study on male circumcision demonstrates the potential benefits of decreasing transmission of HIV, trichomoniasis, and bacterial vaginitis to female sexual partners.


The first systematic review of male circumcision and ulcerative STIs strongly indicates that circumcised men are at lower risk of chancre and syphilis with less association in the reduction of HSV-2.


The first randomized controlled intervention trial of male circumcision which demonstrated a 60% reduction in HIV incidence among the intervention group compared with the control arm. Even after controlling for behavioral factors and health-seeking behavior, the protection was 61% (95% CI 34–77%).


An editorial on Auvert et al’s ‘Randomized, controlled intervention trial of male circumcision’ [19*], discussing its results and policy implications.


This paper provides additional histologic evidence that the densities and positions of HIV target cells in the foreskin of circumcised Kenyan men indicate that the inner mucosal surface of human foreskin contains cells that make it highly susceptible to HIV infection.


Histologic study providing a possible anatomical explanation for the epidemiologically observed protective effect of male circumcision. This paper provides the biological plausibility for circumcision and its protective effect. This paper provides three possible mechanisms to explain why circumcision may protect men from HIV acquisition, including the induction of a mucosal immune response in the presence of repeated antigen stimulation.


This paper describes the acceptability of male circumcision, which was found to vary by region but in general was acceptable if they were safe, affordable, and confidential.


An important paper that illustrates that if circumcision is performed by unlicensed circumcisers in unsterile conditions, the procedure can lead to life-threatening or lethal consequences.


35 Wise J. Demand for male circumcision rises in a bid to prevent HIV. Bull World Health Organ 2006; 84:509–511.


This letter provides an alternative view based on theoretical calculations and empirical evidence that circumcision is unlikely to have a major public health impact primarily due to the fact that achieving universal male circumcision is likely to be more difficult than universal vaccination.


This editorial discusses the ethical issues surrounding the study by Auvert et al. [19*] and why the DSMB stopped the study early.


A paper that discusses the legal implications of routinely performing circumcisions on infants as a public health measure.


Using the results from the South African randomized controlled trial of circumcision, the authors modeled the impact of expanding male circumcision as a public health intervention. Over the next 10 years in sub-Saharan Africa, male circumcision could avert 2.0 million new HIV infections and 0.3 million deaths.


Postexposure prophylaxis after sexual exposure to HIV
Michelle E. Roland

Purpose of review
HIV postexposure prophylaxis is often recommended following potential sexual exposure to HIV. Recent data address the effectiveness of postexposure prophylaxis and prevention counseling, cost-effectiveness, antiretroviral options, challenges with nonoccupational postexposure prophylaxis among adolescents and children and following sexual assault in high HIV prevalence areas, and a successful program in Amsterdam.

Recent findings
Postexposure prophylaxis is not completely protective. Seroconversion may result from antiretroviral failure or from ongoing exposures. Postexposure prophylaxis associated risk reduction counseling results in reductions in subsequent risk behavior. Programs that target outreach and limit prescriptions to those with exposure sources who are at risk of being HIV infected are cost-effective. Less restrictive guidelines result in more prescriptions for low-risk exposures; this practice is not cost-effective. The ideal antiretrovirals for postexposure prophylaxis use have not been established. Tenofovir has several attractive properties. Developing systems to support the effective delivery of postexposure prophylaxis among children and adolescents and following sexual assault in high HIV prevalence, resource limited settings is challenging.

Summary
Numerous national and international guidelines recommend postexposure prophylaxis following potential sexual exposure to HIV. Maximizing adherence and minimizing subsequent HIV exposures will be critical to enhancing the effectiveness of this HIV prevention intervention.

Keywords
antiretroviral drugs, HIV, postexposure prophylaxis, prevention

Introduction
HIV postexposure prophylaxis (PEP) is often recommended following potential sexual exposure to HIV [1–13]. Guidelines differ, however, regarding recommendations when the HIV status of the exposure source is unknown, the type and number of antiretroviral agents to use, and suggested laboratory monitoring. Balancing antiretroviral potency, drug resistance considerations, ease of administration, tolerability, adherence, access and cost to identify the ideal PEP regimen remains a challenge. Recent studies address antiretroviral choices in the context of resistance prevalence, toxicity and medication adherence, and specifically consider the drugs tenofovir, lopinavir/ritonavir and nevirapine [14,15,16,17,18,19].

PEP efficacy following sexual exposure has never been tested. Recent reports of seroconversions suggest that it is not completely effective [20]. Seroconversion following PEP use may result from antiretroviral failure or from ongoing exposures. The important concern that PEP availability may cause harm by reducing primary prevention efforts has been addressed in recent studies [21,22,23]. When provided with intensive risk reduction counseling, PEP users report overall reductions in subsequent risk behavior [21]. Even in the absence of specific risk reduction counseling, risk behaviors have been reported not to increase [23]. The optimal counseling intensity in different settings has not yet been established, nor have the cost implications been addressed.

PEP programs that target outreach and limit prescriptions to those with exposures that could transmit HIV and exposure sources who are at risk of being HIV infected are cost-effective [24,25]. The publication of guidelines tends to result in more prescriptions for low-risk exposures [26,27,28,29]. This practice was not cost-effective in France after the introduction of liberal prescribing guidelines [27]. Developing acute care and follow-up systems to support the effective delivery of PEP related services, especially following sexual assault in high HIV prevalence, resource limited settings is

Abbreviations
MSM men who have sex with men
PEP postexposure prophylaxis
PMTCT prevention of mother to child transmission
SIV simian immunodeficiency virus

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challenging, although some successes have been reported [6,30,31,32,33]. Specific challenges facing children and adolescents and their healthcare providers have been described recently [32,34,35]. The World Health Organization (WHO) has undertaken the process of developing guidelines for PEP use in resource limited settings (see background materials http://www.hivinsite.com/pdf/p01-kb-new/kbr-07-02-07-roland.pdf). Enhancing medication adherence and follow-up for HIV testing and appropriate trauma or HIV risk reduction counseling will require creative integration of these services into existing HIV prevention, care and treatment and sexual assault policies, and service delivery systems.

Does postexposure prophylaxis work following sexual exposures?

There is no completed or ongoing study evaluating PEP efficacy following sexual exposure. The only efficacy study of PEP use in adult humans is in the context of occupational healthcare worker exposures, where zidovudine use was associated with an 81% reduction in the risk of acquiring HIV infection [36]. Two recent prospective studies have shown that postexposure antiretroviral use in infants of untreated HIV-infected mothers reduces the risk of HIV infection [37,38]. The relative contribution of the postexposure component of combined pre, intra and postpartum antiretroviral interventions to prevention of mother to child transmission (PMTCT) was previously unknown. These studies, as well as the occupational PEP study and numerous studies in animal models, support the biological plausibility of nonoccupational PEP efficacy [18,39,40].

Initial descriptions of PEP user cohorts in the United States, Europe, Australia and Brazil suggested that HIV seroconversion following nonoccupational PEP use was rare and was always associated with ongoing exposure risk [23,41–44]. A recent report describing HIV testing results 3 months following PEP initiation in 702 PEP users in San Francisco showed a sobering seven seroconversions [20**]. All of the seroconverters had presented for PEP following the highest risk sexual behavior – receptive anal intercourse; 50% of the nonseroconverters presented with this risk indication. This statistically significant difference may explain why PEP failed in some of these individuals or may be a marker of overall higher risk behavior in this group. Three seroconverters did not know the HIV status of their sexual partner. Thus, in a high HIV prevalence context [e.g. men who have sex with men (MSM) in San Francisco], sources of unknown HIV status should be assumed to be HIV infected when assessing HIV transmission risk and PEP indications. There was a nonstatistically significant trend towards later PEP initiation among the group that seroconverted, although some initiated PEP within 24 h of exposure. Adherence ranged from perfect to poor. Approximately half of this group reported no subsequent unprotected intercourse; it is presumed that infections in these individuals resulted from PEP failure. The others may have become infected from subsequent risk behaviors and thus may represent a failure of risk reduction counseling to prevent HIV infection.

There will probably never be a randomized, controlled efficacy trial of PEP following sexual exposure. A placebo control would be unethical given the supporting data outlined above in the areas of occupational PEP, PMTCT and animal simian immunodeficiency virus (SIV) transmission models. The per-contact transmission rate of HIV is very low, ranging from less than 0.1% to approximately 3%, depending on exposure type. Furthermore, sexual exposures rarely occur as isolated events. As a result, the sample size required to demonstrate the efficacy of an intervention aimed at preventing HIV infection from a single exposure is in the tens of thousands. Such a study would be prohibitively complicated and expensive given the impact of the question. A case-control study is challenging to design without established cohorts of exposed individuals who do and do not access PEP, all of whom provide comprehensive behavioral data and undergo regular HIV testing.

Behavioral impact of postexposure prophylaxis availability and programs

Recent discussions in the medical literature have raised the potential harm associated with PEP following sexual exposures if its use is associated with a subsequent reduction in primary prevention efforts [22**]. A previous study among a high-risk cohort of young MSM in Brazil who were all given PEP starter packs to initiate if an eligible exposure occurred suggested that risk behaviors did not increase among PEP users as a result of PEP access [23]. The initial PEP program in San Francisco provided five sessions of risk reduction counseling to address this concern and found that nearly three-quarters of the cohort reported a reduction in unprotected intercourse following PEP use and only 14% reported an increase [21]. Recognizing the resource implications of such an intervention, the San Francisco group subsequently conducted a randomized controlled trial comparing the effectiveness of the intensive five-session counseling intervention with a two-session strategy. In preliminary, unpublished analyses, the two interventions were equivalently effective in reducing subsequent unprotected intercourse, additional PEP use and HIV seroconversion [45]. The more intensive intervention, however, was more effective in the 20% of clients who presented with the highest level of baseline risk. Thus, programs that provide less intensive counseling interventions to most clients can enhance their effectiveness with a baseline risk assessment and referrals for more intensive prevention interventions for riskier individuals.
Only targeted postexposure prophylaxis programs are cost-effective

Early models and opinion pieces considered the cost-effectiveness of PEP given specific exposure characteristics, accounting for relative per-contact transmission rates and source HIV status. They found that only the highest risk sexual exposure circumstances would be cost-effective. Some concluded that PEP should therefore only be offered following receptive anal intercourse with a source who was known to be HIV infected.

Programs that provide PEP following sexual exposure, however, usually offer PEP following all exposure types that may potentially transmit HIV, including insertive anal intercourse and both receptive and insertive vaginal exposures. The per-contact transmission rates associated with these exposure types are similar to the 0.3% transmission rate associated with occupational needle stick exposures; receptive anal intercourse transmission rates are approximately an order of magnitude higher. Many programs also consider the likelihood of the exposure source having HIV infection when their status is unknown, based upon the local epidemiology and risk factors of the source, rather than limiting PEP to those whose exposure source is known to be HIV infected.

A cost-effectiveness analysis using actual program costs found that the San Francisco program was cost effective overall [24]. PEP use following receptive anal intercourse with a known HIV-infected partner was actually cost saving. Of note, this program targeted outreach to those at highest risk of HIV transmission, namely MSM [41]. When this analysis was extended to 96 US metropolitan areas, accounting for local epidemiology, similar PEP programs were estimated to be cost-effective in 94 areas [25]. In contrast, a recent study found that the French PEP program was not cost-effective [27**]. French guidelines recommend that clinicians consider ‘the perception of the risk leading a person to request prophylaxis’ when determining PEP eligibility. Similar to Canadian and American experiences suggesting that PEP guidelines result in increased prescribing for low-risk exposures, the majority of prescriptions in the French setting were for lower risk exposures [26,28,29]. The cost-effectiveness was similar in the US and French studies when looking at specific exposure types, but program cost-effectiveness depends on the mix of exposure types within the program. In order to be cost-effective, PEP policies and programs should target outreach to individuals at highest risk of HIV exposure based upon local epidemiology [46]. Further, clinicians should be encouraged to adhere to evidence-based prescription criteria rather than determining HIV transmission risk based upon the client’s degree of concern.

How many and which medications should be used for postexposure prophylaxis?

An ideal PEP medication regimen would have no side effects, drug interactions, or contraindications in any population, work as well as or better than any alternative regimen, be easy to take and cost as little as possible. While there are no randomized studies to inform relative efficacy, side effect or adherence rates, the following points should be considered when choosing a PEP regimen.

First, there is no consensus about whether two or three drugs should be used for standard nonoccupational PEP regimens [1–13]. Some guidelines recommend the same number be used in all circumstances and others recommend three drugs only with exposures that are more likely to transmit HIV infection. A modeling exercise in the context of occupational PEP considered relative toxicity, medication discontinuation rates and efficacy at various community antiretroviral resistance rates [14]. The authors concluded that two-drug regimens were often preferable to three-drug regimens, especially when the resistance prevalence was low. Of course, when antiretroviral drug resistance is known or suspected in a specific source virus, the regimen should be adapted to maximize the use of potentially suppressive agents.

There is also no consensus about which drugs to use, although some agents are not recommended for PEP. Full course nevirapine has caused serious and sometimes fatal hepatic and cutaneous reactions in HIV-uninfected individuals when used for PEP [15,47]. Thus, nevirapine is contraindicated for PEP except in unique situations in which resistance and other considerations are compelling [47]. The safety and feasibility of using an abbreviated course of nevirapine, similar to that used in PMTCT, has not been firmly established. A retrospective analysis of 120 clients who received two nucleoside analogues plus 4 days of nevirapine (200 mg daily) did not reveal any serious nevirapine associated toxicities [17]. The long half life of nevirapine and the efficacy of a single dose in PMTCT raises the possibility of the adjunctive use of single dose nevirapine in addition to the standard 28-day combination PEP regimen, although the safety and effectiveness of this approach have not been evaluated [37,38*,48*,49].

Efavirenz should not be used in women who are or may become pregnant while on PEP. The risk of pancreatitis associated with didanosine, and its relative contraindication in pregnancy, should also be taken into consideration. This risk should be weighed against the very low risk of HIV transmission associated with many sexual exposures.

There is a great deal of interest in the use of tenofovir in PEP regimens based on the convenience of daily dosing,
relatively minor side effects, and partial effectiveness in animal models of pre and postexposure prophylaxis [18*,19*,39,50*]. New York state guidelines recommend adding tenofovir as a third agent in combination with zidovudine and lamivudine. Several studies have attempted to compare the tolerability and completion rates of regimens with different protease inhibitors or different nucleoside/nucleotide analogues, including regimens with and without tenofovir [19*,51]. While there are suggestions that tenofovir-containing regimens may be better tolerated than zidovudine or protease inhibitor-containing regimens, these studies report sequential rather than randomized, controlled regimen use. The authors of a study evaluating side effects and completion rates with the use of a lopinavir/ritonavir-containing PEP regimen suggested that this protease inhibitor combination may be better tolerated than indinavir or neefinavir-containing regimens based on previously reported data [16*].

Although many guidelines continue to recommend fixed dose combination zidovudine–lamivudine as the nucleoside backbone or complete PEP regimen, it is reasonable to consider new drug development and advances in formulation when choosing PEP regimens. Zidovudine was included in all initial regimens because it is the only agent that was ever evaluated in an efficacy study – the healthcare worker case control study [36]. There are no compelling data to suggest, however, that some nucleoside analogues are likely to be more effective than others. The fixed dose combination of tenofovir and emtricitabine is an attractive choice in terms of ease of administration and presumed toxicity profile. Likewise, if a third drug is used, it is reasonable to consider a three-nucleoside regimen containing tenofovir and a thymidine analogue (i.e. zidovudine or stavudine) or a protease inhibitor. If atazanavir is considered, concomitant proton pump inhibitor – and possibly H2 blocker – use should be avoided. In resource-limited settings, drug procurement is an important consideration. Antiretroviral agents used for the treatment of HIV should also be used for PEP rather than developing PEP protocols that require access to alternative agents.

**What laboratory testing is required for people using postexposure prophylaxis?**

Almost all guidelines, with the exception of California’s, recommend routine safety laboratory testing, usually including complete blood count and liver enzymes. Serious side effects requiring hospitalization, and laboratory abnormalities, have been reported with various PEP regimens. These have often been in individuals using three-drug regimens. In our prospective studies of approximately 900 individuals using mostly two-drug regimens in San Francisco, we have seen no serious laboratory toxicities [41,45]. Thus it is probably reasonable to restrict laboratory testing to the evaluation of symptoms rather than as routine screening tests in otherwise healthy individuals using PEP.

**HIV RNA testing should not be used to detect asymptomatic preseroconversion acute HIV infection in postexposure prophylaxis users**

A concern of early PEP providers was that two-drug regimens would be provided to clients who tested HIV antibody negative at presentation but were in the preseroconversion window period for HIV infection. Thus, some instituted routine HIV RNA screening at baseline. Unfortunately, this practice resulted in numerous false positive test results [52]. Investigators repeated HIV RNA testing in batches using three different tests and calculated the specificity of each test when run in batch, and, when data were available, in real time. Although polymerase chain reaction (PCR)-based tests performed better in batched testing than branched DNA-based tests, none had an acceptable positive predictive value. The prevalence of the preseroconversion condition is very low, even with very generous assumptions about HIV incidence and the duration of the window period. The likelihood of false positive test results with asymptomatic individuals exposed within 72 h is high.

There may be confusion given the success of recent programs that use HIV RNA based testing to screen individuals who are having routine antibody testing [53*]. These programs have much higher specificity and a resulting higher positive predictive value because plasma pooling effectively increases the detection limit required to identify a positive sample. Current HIV RNA based tests available for clinical laboratory use are designed to maximize sensitivity at the cost of specificity. Thus, programs that pool samples for HIV RNA screening are effective in detecting asymptomatic individuals in the window period, but routine real time individual sample screening of clients presenting for PEP is not recommended [52,54,55].

**Additional differences among guidelines**

Current guidelines provide different recommendations regarding acceptable timing of PEP initiation and distinctions based upon knowledge of the exposure source’s HIV status. Difference in recommendations regarding antiretroviral number and type and laboratory monitoring have been discussed previously. All guidelines recommend that PEP be taken for 28 days. This duration was superior to two shorter-course regimens in a single animal study [40].

Almost all recommend that PEP be initiated as soon as possible within 72 h. This cut-off was selected based on animal models of intravaginal SIV transmission and the timing of detection of plasma viremia as well as PEP
models that show no efficacy after 72 h. New York state guidelines have a cut-off of 36 h based on incremental reduced efficacy in animal models with increasing passage of time between exposure and PEP initiation [39,40]. In the initial San Francisco study, the median time to PEP initiation was 33 h, despite 24 h access to a telephone prescription [41]. Thus, with a 36 h limit nearly half of these individuals would have been ineligible for PEP. Some guidelines allow for consideration of PEP initiation in very high-risk situations after 72 h.

Some guidelines recommend PEP for potential exposures with both known HIV-infected sources and those at high risk of being HIV infected based upon local epidemiology and source risk factors. Others recommend PEP routinely only for exposures from infected sources and recommend a case-by-case evaluation of sources whose HIV status is unknown. There is a potential risk that providers will choose to offer PEP only to those with a known infected source if they are not comfortable with assessing HIV risk in sources of unknown HIV status. Seroconversions have been reported following exposures with sources of unknown HIV status who were at high risk of being HIV infected [20**,27**,46].

Challenges and successes in postexposure prophylaxis service delivery

There are few settings in which PEP is routinely accessible throughout a community. One exception is in Amsterdam, where PEP is available 24 h a day though three hospital emergency departments and the municipal health service, with a dedicated on-call doctor and a clear follow-up system [56**]. PEP is provided following sexual contact, nonhospital-based healthcare provider exposures, exposures during nonhealthcare work, abandoned needle exposures, and other community exposures. Between 2000 and 2003, 377 nonoccupational exposures were recorded, including 172 sexual exposures. There was no clear evidence that PEP availability for consensual sexual exposures resulted in an increased demand for PEP or an increase in unprotected intercourse. This system may serve as a useful model for other communities to consider.

Postexposure prophylaxis following sexual assault

Typical of previous reports from North America and Europe describing a similar time frame, a recent description of PEP use in an urban US emergency department between 1999 and 2002 suggested that PEP was offered to about half of those who were eligible, accepted by 45% of them, and completed by 21% of those [57,58,59*,60,61]. Only 8% of 117 clients seen in a sexual assault service in Sydney in 1999–2000 were offered PEP [33*]. Unfortunately, there are no reports describing more contemporary trends in PEP use in developed countries in the context of adult sexual assault services. It is conceivable that practices have changed significantly as US and European guidelines have developed and providers have become more comfortable offering and managing PEP.

A prospective, observational study of PEP use following sexual assault was conducted between 1997 and 2001 in an academic hospital in Sao Paulo, Brazil [31**]. PEP was offered to and accepted by 278 of 347 individuals. In contrast to some studies of PEP following consensual exposures, and similar to others describing PEP following sexual assault, the median time to PEP initiation was only 13 h [41,62]. Two or three-drug regimens were offered for exposures considered to be of moderate or severe risk for HIV transmission, respectively. Approximately half received two and half received three drugs. Sixty percent completed the PEP regimen, with those receiving two drugs more likely to complete than those receiving three drugs (\(P = 0.01\)). Side effects were more common among those using three drugs (95% versus 66%; \(P < 0.01\)). As this was not a randomized intervention, other factors may be associated with some of these differences, including the emotional trauma associated with more severe exposures. All severe side effects requiring hospitalization, however, occurred in those receiving three drugs, including Steven’s-Johnson syndrome, nephrolithiasis and severe gastrointestinal symptoms. Only 52% completed 6 months of follow-up; no HIV seroconversions were detected.

Kenya is at the forefront of establishing comprehensive, multisectoral, national policies and service delivery systems to provide PEP following sexual assault [5,32*]. A sexual assault care algorithm has been implemented at several district hospitals in conjunction with established HIV testing, care and treatment programs. Training is provided to doctors, clinical officers and nurses. To facilitate rapid access, PEP, sexually transmitted infection prophylaxis and emergency contraception are provided after hours in casualty. Significant challenges remain in the implementation of this program, particularly with facilitating the initial post-casualty and longer-term follow-up care. The high proportion of children seeking care after rape has necessitated the development of weight band-based guidelines for the appropriate pediatric dosing of PEP medications. In addition to logistical issues, the psychological impact on care providers of looking after these children is also of concern.

A retrospective review of PEP use at a children’s hospital in Cape Town, South Africa focused on obstacles to PEP accessibility and follow-up [34*]. Only 60% of 115 children who were seen over a period of less than a year and a
half presented within 72 h and were given PEP. Prior to coming to this hospital, 44% went to a police station or a health center that did not provide PEP, resulting in delays in PEP initiation. The authors propose that PEP should be available at as many health centers as possible to reduce delays in initiation. Forty per cent did not return for any HIV testing, and only 23% were tested at 6 months.

Poor follow-up rates have been reported in all retrospective reviews of PEP use, whether in children or adults, or whether following consensual or nonconsensual exposures. In contrast, prospective studies that incorporate proactive follow-up and tracing systems report substantially higher follow-up rates, even among sexual assault survivors [62]. The Amsterdam program, with a clear follow-up protocol, also reported much higher retention and follow-up rates [56**]. If policy makers and service providers value retention and follow-up in order to enhance adherence during the PEP dosing period and follow-up HIV testing, they will have to develop proactive follow-up systems. Barriers including distance, travel costs, lack of access to food and child care needs must be addressed to maximize the potential utility of PEP.

A recent South African study suggests that women were more concerned about having access to PEP and to a sensitive healthcare provider who can provide counseling than having a shorter travel time to access sexual assault care services [30**]. In addition, they preferred more follow-up visits for counseling over fewer visits. They preferred having all the medication dispensed at one time. Among the many factors explored, access to PEP was the most important to the 319 women (half who had accessed postassault services and half from the surrounding community who had not) interviewed in 2003 and 2004 in urban and rural South Africa. Women wanted to have access to HIV testing first, but preferred a service that would provide PEP without testing to a service that did not provide PEP at all.

Even in the best of circumstances with creative and well resourced service delivery systems, some populations are likely to continue to present difficult challenges. For example, almost half of adolescents receiving care in two urban emergency department-based sexual assault services between 2001 and 2003 had a prior psychiatric diagnosis [35*]. Many were unsure about what had happened, including if condoms were used, and a fifth had blacked out during the assault. Of 97 patients who were referred for follow up after receiving PEP, 38% attended at least one follow-up visit and 13% completed the course. Finally, sexual assault survivors may engage in ongoing unprotected intercourse that puts them at risk for HIV infection. In a preliminary analysis from Cape Town, nearly two-thirds of adult and adolescent sexual assault survivors reported unprotected intercourse 6 months after the assault, and most of these were with partners whose HIV status was unknown [62]. Thus, focusing exclusively on the assault without considering the context of HIV risk may lead to missed HIV prevention opportunities.

**Conclusion**

Numerous national and international guidelines recommend the use of PEP following potential sexual exposure to HIV infection. There is no consensus about the ideal PEP regimen, specific safety laboratory testing, or indications for PEP when the HIV status of the exposure source is unknown. The World Health Organization is in the final review stages of guidelines that will address occupational and nonoccupational PEP use in resource-limited settings. The consensus reached in these guidelines should inform future policy decisions in all settings.

PEP has been utilized following consensual exposures – mostly in high-risk MSM – in North America, Europe, Australia and Brazil. When provided with prevention counseling, there is no evidence that PEP availability results in increased risk taking. Programs that target high-risk populations have been cost-effective. In contrast, untargeted programs that provide PEP following exposures with source partners who are unlikely to be HIV infected are not cost-effective. Some PEP users have seroconverted, reflecting the failure of either PEP to prevent initial infection or of prevention counseling to reduce subsequent risk. PEP programs should target those at highest risk and should focus on a comprehensive approach to HIV prevention beyond providing PEP for a single exposure.

PEP following sexual assault is used in both low and high HIV prevalence settings. Rates of offering and accepting PEP have been low in most low prevalence settings except in France, although contemporary data have not been published. Previously identified barriers to PEP acceptance in the urban US include homelessness and race [60]. A renewed focus on identifying and intervening in such barriers is critical if access to PEP is to be equitable. Follow-up and PEP completion rates have been low in all settings that do not utilize a proactive follow-up system, including telephone contact, home visits and transportation. Retention systems and interventions aimed at maximizing adherence and minimizing subsequent HIV exposures are critical to enhancing the potential effectiveness of this HIV prevention intervention in all circumstances. The experience in Amsterdam may be a useful model that appears to facilitate access and maximize follow-up for all PEP-eligible individuals.
Postexposure prophylaxis Roland

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 90).


2 California Task Force on Non-Occupational PEP and the California Department of Health Services Office of AIDS. Offering HIV postexposure prophylaxis (PEP) following nonoccupational exposures: recommendations for healthcare providers in the state of California. Sacramento, California; 2004.


11 New York State Department of AIDS Health Institute. HIV prophylaxis following nonoccupational exposure including sexual assault; 2004.


23 Review editorial raised the concern that providing PEP following consensual sexual exposures may be harmful by causing erosion of primary prevention strategies such as condom use.


32 PEP was initiated quickly in a prospective study of sexual assault survivors in Sao Paulo, Brazil. A two-drug regimen was prescribed for moderate-risk exposures and a three-drug regimen for high-risk exposures. Two-drug regimens were associated with higher completion rates and fewer side effects, although without randomization it cannot be concluded that other factors, including higher levels of emotional distress, did not contribute to this difference.
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   This paper described the early experiences with a Kenyan PEP program. Un-
   anticipated high rates of child sexual assault victims have raised concerns about
   pediatric dosing and the psychological needs of healthcare providers. Poor follow-
   up rates will require modifications in the service delivery system.

33 Templeton DJ, Davies SC, Garvin AL, Garsia RJ. The uptake of HIV post-
• exposure prophylaxis within a sexual assault setting in Sydney, Australia. Int J
   reports extremely low rates of offering PEP.

34 Hachey M, van As AB. HIV postexposure prophylaxis in victims of child sexual
   Delays in PEP initiation for children in Cape Town resulted from the initial
   presentation at a police station or healthcare facility that did not provide PEP.
   The authors propose that PEP should be broadly available in the health sector.
   Facilitating PEP initiation with a stat dose and then making appropriate referral
   for further assessment and follow up is important. Upcoming WHO guidelines
   will address these issues.

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Purpose of review

The HIV virus has been present in our society for more than two decades. Although there was originally much academic interest in the possibility of prosecuting for the reckless transmission of HIV in England and Wales, it was thought impossible by many (including the government) under existing legislation. The first prosecution in England in 2003 (following the first UK prosecution in 2001, in Scotland) provoked a great deal of surprise not least in the HIV voluntary sector, which has since been campaigning for the cessation of such prosecutions. This review examines the law in this area and provides an understanding of the development of the ethical and other issues involved.

Recent findings

Since 2003 there have been seven further convictions for the reckless transmission of HIV in England and Wales. These prosecutions have led to several responses that are discussed here and the current developments in this area outlined.

Summary

Whether it is right to prosecute the reckless transmission of HIV remains a controversial, pressing question. This brief article aims to dissect and question the relevant issues and help inform this debate.

Keywords

criminalization, HIV transmission, public health

Introduction

From the outset, HIV infection in the West has been tackled differently from other significant infectious diseases. The already marginalized groups then predominately affected (particularly gay men) were themselves instrumental in shaping societal responses. A ‘rights-based’ approach was developed that promoted respect for the rights and privacy of those affected. This served to shape the public health approaches to HIV infection and to counter the coercive measures proposed in other quarters [1]. The UK government introduced noncoercive measures such as voluntary testing, pretest and posttest counselling, mass education, and ‘The national strategy for sexual health and HIV’ [2] with the stated goals of increasing testing and treatment. Whether this ‘exceptionalist’ approach should be maintained, when considering the issues arising from the recent prosecutions for reckless HIV transmission, is open to debate.

The view of the UK government

In Europe the first prosecution for the transmission of HIV took place in 1988, and since that time there have been more than 130 convictions (in at least 36 member states of the European Union including Armenia, France, Switzerland, and Sweden) (Terence Higgins Trust and Global Network of People Living with HIV/AIDS Survey of ‘Criminalisation of HIV Transmission in Europe’; www.gnpplus.net/criminalisation/results1.shtml; note, however, that of the 600 questionnaires sent out in this survey, only 87, or 14.5%, were returned.) The sentences passed for such offences vary from fines, correctional labour (Armenia), isolation ranging from 6–9 months (up to 7.5 years in one case in Sweden), and most commonly prison sentences.

Naturally there has always been much academic interest in the UK as to the possibility of prosecuting for the transmission of HIV infection, whether it be intentional or reckless (i.e. knowing one is infected, being aware of a risk of transmitting that infection, and nonetheless taking that risk). For some time, it was thought impossible by many, including the government, to prosecute under existing legislation by virtue of the fact that previously the courts in R v Clarence [3] and other cases had interpreted the relevant legislation (sections 18 and 20 of the Offences Against the Person Act [OAPA] 1861) as requiring immediate harm to come about as the result of some kind of blow.
In 1998, the government proposed a new OAPA bill to plug this gap. The bill proposed creating an offence of intentionally transmitting an infection. The government made it plain that the law should not discriminate against those who have infections such as hepatitis or HIV by the creation of infection-specific offences. The bill was never enacted, however. In 2000 the government reiterated the view that individuals should not be prosecuted for transmission of infection unless transmission was intentional [4].

**Prosecutions in the UK**

Since the decision in *R v Claverton*, however, the law has developed and the requirement that there be immediate harm resulting from a blow has been abandoned. For example, the law now allows prosecution under OAPA 1861 for assaults causing psychological harm caused by nuisance telephone calls [5]. This development has paved the way for its subsequent application to the prosecution for the transmission of HIV infection. Moreover, contrary to the intentions expressed by the government in 1998 and in 2000, there have been several prosecutions for reckless transmission. See Table 1 for the elements of the offences of reckless and intentional transmission [6*].

The first UK prosecution took place in Scotland in 2001. Stephen Kelly was prosecuted (under Scottish law) for reckless endangerment to a female partner by transmitting HIV (*HMA v Kelly*, unreported, 23 February 2001, Glasgow). Since then there have been eight successful (and one unsuccessful) prosecutions in England and Wales for the reckless transmission of HIV brought under section 20 of OAPA 1861 (Table 2).

In two of these cases the defendant was originally charged with intentional transmission but was found guilty of the lesser offence of reckless transmission. Despite misleading press reports describing ‘deliberate’ transmission of infection, there have been no successful prosecutions for intentional transmission. In six cases, the defendant pleaded guilty. The two cases that went to trial, *R v Dica* [7] and *R v Konzani* [8], were both referred to the Court of Appeal. There has been one acquittal (August 2006) because the phylogenetic analysis failed to establish beyond reasonable doubt that person A infected person B (rather than e.g. both being infected by person C). There is now concern that in some of the previous cases the defendant pleaded guilty on advice that the scientific evidence ‘proving’ transmission was unquestionably conclusive.

As a consequence, experts in this field are in the process of producing a report that will address the minimal requirements for virologic evidence to be admitted in criminal cases and will assist with the correct interpretation of such evidence. It is hoped this will be available in November 2006 (personal correspondence from Dr Anna Maria Geretti, Virology Department, Royal Free Hospital, London).

We should note that the law as it stands also applies to sexual transmission of other serious infections. No successful prosecutions have been brought for transmission of other infections, but two cases involving genital herpes and hepatitis B infection have been attempted [9].

**R v Dica**

Dica was convicted in 2003 of two counts of inflicting grievous bodily harm contrary to s20 of OAPA 1861. He appealed to the Court of Appeal. The Court of Appeal recognized the distinction between consent to sex and consent to risk of infection. The court ruled that when a person has knowledge of the other’s HIV status and nonetheless has sex with him or her, then consent to the risk of infection with HIV can be implied and will be a defence to the charge under OAPA 1861. In taking this approach, the court intended to strike a balance between criminalizing behaviour that it thought deserved prosecution and maintaining personal autonomy within the sphere of private sexual relations. Dica’s conviction was quashed, but he was convicted in the retrial because the jury disbelieved him on the question of whether he had told his partner that he was HIV positive.

**R v Konzani**

Konzani was convicted in May 2004 of three counts of inflicting grievous bodily harm by transmitting HIV infection to three women contrary to s20 of the OAPA 1861. The defence at trial was simply that by having unprotected sex the complainants had consented to the risk of contracting HIV infection. The defendant was

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Table 1  ‘Reckless’ and ‘intentional’ transmission of HIV

<table>
<thead>
<tr>
<th>Reckless Transmission</th>
<th>Intentional Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The defendant was infected with a sexually transmissible infection</td>
<td>4. As a result of the defendant’s behaviour, the victim suffered grievous bodily harm (i.e. really serious harm)</td>
</tr>
<tr>
<td>2. The defendant knew he or she had that infection</td>
<td>5. The victim did not know of the defendant’s infection and did not give informed consent</td>
</tr>
<tr>
<td>3. The defendant was reckless (the person knew that he or she was infected, was aware of a risk of transmitting that infection but took that risk)</td>
<td><em><a href="http://www.cps.gov.uk/news/consultations/sti_policy.html">http://www.cps.gov.uk/news/consultations/sti_policy.html</a>.</em></td>
</tr>
</tbody>
</table>
Table 2 Prosecutions for the reckless transmission of HIV in the UK

1. Stephen Kelly 2001
   Defendant: White heterosexual man who acquired HIV in prison through sharing injecting equipment
   Charge: ‘Reckless endangerment’ because he was found to have transmitted HIV to a female partner
   Sentence: 5 years

2. Mohammed Dica 2003
   Defendant: Kenyan man with refugee status
   Charge: Case went to the Court of Appeal 2004 (see text) and was then followed by three retrials; on the third retrial he was convicted of ‘recklessly inflicting grievous bodily harm under s20 OAPA 1861’ for the HIV infection of one woman
   Sentence: 4.5 years

3. Kouassi Adaye 2004
   Very little information is available as he pleaded guilty
   Defendant: The papers reported that Adaye was a 40-year-old male asylum seeker from the Ivory Coast
   Charge: Plead guilty to ‘recklessly inflicting grievous bodily harm under s20 OAPA 1861’ for the HIV infection of a woman in Liverpool
   Sentence: 6 years (this sentence includes the sentences for 20 other non-HIV-related offences)
   Note: Adaye had never had an HIV test (see text re: subjective recklessness)

4. Feston Konzani 2005
   Defendant: 28-year-old man, originally from Malawi (the Asylum service had placed him in Middlesborough)
   Charge: Case went to the Court of Appeal; defendant found guilty of ‘recklessly inflicting grievous bodily harm under s20 OAPA 1861’ for the HIV infection of three women
   Sentence: 10 years

5. Paulo Mathis 2005
   Defendant: 38-year-old Portuguese migrant man
   Charge: Plead guilty to ‘recklessly inflicting grievous bodily harm under s20 OAPA 1861’ for the HIV infection of one woman
   Sentence: 3.5 years (died in January 2006)

6. Anonymous Welsh woman 2005
   Defendant: 20-year-old white heterosexual woman
   Charge: Plead guilty to ‘recklessly inflicting grievous bodily harm under s20 OAPA 1861’ for the HIV infection of her male partner
   Sentence: 2 years in a young offenders institute

7. Derek Hornett 2005
   Defendant: 44-year-old white man from Devon
   Charge: Plead guilty to ‘recklessly inflicting grievous bodily harm under s20 OAPA 1861’ for the HIV infection of an 82-year-old woman
   Sentence: 3 years, 3 months

8. Mark James 2006
   Defendant: White gay man
   Charge: Plead guilty to ‘recklessly inflicting grievous bodily harm under s20 OAPA 1861’ for the HIV infection of a man
   Sentence: 40 months

   Defendant: 43-year-old white heterosexual woman
   Charge: Plead guilty to ‘recklessly inflicting grievous bodily harm under s20 OAPA 1861’ for the HIV infection of one man
   Sentence: 2 years, 10 months

convicted and sentenced to a total of 10 years’ imprisonment. He appealed to the Court of Appeal and his convictions were upheld by the Court of Appeal. In keeping with R v Dica, Judge LJ said that there was a distinction between the taking of general risks associated with sex and the giving of informed consent to the risk of HIV infection. The court also made it clear that informed consent can arise from situations other than direct disclosure of HIV status by the person concerned – e.g. if the person were informed by someone else about the partner’s HIV status or if the person knew the defendant when he or she was in hospital for HIV-related illness. Both these examples raise their own questions, but if either was asserted by the defendant or on his behalf it would be up to the prosecution to disprove that the complainant knew about the partner’s HIV status.

The Court of Appeal in R v Konzani also clarified two further matters that relate to the necessary state of mind of the defendant before he or she can be convicted. The first relates to the precise nature of the mental element of the offence of reckless transmission. Judge LJ clarified that recklessness is established if the defendant subjec-

\textit{tively} knew or foresaw that the complainant might suffer bodily harm from HIV infection and yet chose to take that risk. It follows from this that it is not enough to show that the defendant was \textit{objectively} reckless, i.e. that in all the circumstances (e.g. symptoms following unprotected sex with others with HIV infection), the person ought to have known that he or she was HIV positive. Further, when a defendant honestly believes that the complainant has given ‘informed consent’, i.e. agrees to unprotected sex knowing that the defendant is HIV positive, then the defendant would have a defence against the charge. This will be so regardless of whether the complainant gave informed consent. This is similar to rape laws, whereby a defendant is not guilty if he honestly and reasonably believed that the complainant consented to sex.

**Responses to the prosecutions**

Responses to the prosecutions that have taken place over the past 5 years have varied. The press appears to welcome the cases, adopting unhelpful headlines such as ‘AIDS assassin jailed’ (Daily Star, 24 March 2005), for instance. Most legal writers have also responded favourably [10]. The majority of the HIV voluntary sector
agrees with the prosecution of intentional transmission but opposes the prosecution of reckless transmission [11].

**The pros and cons of prosecution**

There are several important issues that need to be considered.

**Duty to avoid harm and respect for autonomy**

Despite the incredible advances in the management of HIV infection, most would agree that contracting HIV still amounts to a ‘harm’. Those in favour of criminalization argue that, according to normal ethical principles, knowingly putting another person at risk of harm is morally culpable and that there is no reason why it should be exempt from the law. Moreover, it is in the public interest to prosecute as such prosecutions not only punish those who have engaged in morally culpable behaviour but also serve to protect the gullible and act as a deterrent to those who might otherwise commit such offences.

Of course, it is true that sex has never been understood to be ‘risk free’, not least because a vast proportion of infection is undiagnosed and those infected may be unaware of their infection status. It follows that reliance on disclosure of known infection is an inadequate way of protecting oneself. Certainly the public health message is that people should be encouraged to take responsibility for their own health, including the avoidance of sexually transmitted infection (or unwanted pregnancy) by the use of protection. This makes good sense, particularly in light of the ‘window period’ for HIV testing and the prevalence of undiagnosed infection, and it is an essential part of the effort to reduce the spread of HIV infection. The fact that a person might be imprudent in not using protection, however, should not be confused with a relinquishing by that person of their right to respect for their autonomy, i.e. the ability to make an informed choice. Western society places great value on the respect for individual autonomy, and it may be argued that when a person with HIV infection does not disclose infection status, he or she thereby compromises the other person’s autonomy without justification.

Some of those involved in the debate nonetheless seek to absolve those who have HIV infection of moral responsibility for its transmission by emphasizing the desirability of taking responsibility for one’s own health. As Weait [12] puts it,

> ...how dare I argue that simply because he knew his HIV+ status he is the one at fault in any socially meaningful sense? I dare because the law ignores my risk taking, my irresponsibility and legitimates my gullibility.

We may well fairly comment on the risk taking and even the gullibility of the person who becomes infected; however, neither logically absolves the person who knows he or she had HIV from the duty not to cause harm to others and not to deprive others of making an autonomous choice.

**Law and morality in the bedroom**

On the face of it, the fact that transmission of HIV occurs in the private realm should not absolve moral culpability. Neither the obligation to prevent harm to another nor the importance of autonomy is diminished by reason of a sexual context. To suggest that these principles may be applied only to nonintimate scenarios [13] is to ignore that the law must often grapple with complex human behaviour. Many intensely private situations are analysed in courts of law, e.g., when there are allegations of rape by a known partner. These cases can be difficult to prove, often turning on one person’s word against another’s, and harrowing for all involved, but that does not mean that rape should not be prosecuted. Similarly, the fact that issues of intimacy, sexual desire, trust, and honesty arise in the context of sexual relations between two persons, one of whom is HIV positive, does not mean that the person who is morally culpable should be exempted from the law. The pertinent question, therefore, is whether there is any other good reason to exempt the transmission of HIV infection from the application of normal ethical principles.

**False reassurance?**

Jack [14] has argued that prosecution might encourage the public to consider that all of the responsibility in relation to transmission is to be borne by the person infected by HIV and that a negative HIV status may be assumed in the absence of disclosure. If this were so, then prosecutions would be highly undesirable because they would likely lead to an increase in the rate of transmission. Whether such law would provide this ‘false reassurance’ is another matter. It is possible, of course, that prosecution for reckless transmission could increase public awareness of the risk of infection.

**Negative impact of prosecutions upon public health**

There are more substantial arguments, militating against prosecution, however, notwithstanding the moral culpability involved. It is argued by many that continued prosecution will give rise to potentially disastrous public health effects.

**Reduction in testing due to fear of prosecution**

Before a person may be convicted of reckless transmission, the law requires the prosecution to prove that at the time the defendant knew of his or her HIV-positive status. A positive test result may not be the only way to prove knowledge, but it is the best evidence. It is at the very least possible if not probable, therefore, that some of those who suspect they may be HIV positive may be deterred from coming forward for testing. At present no
evidence supports (or refutes) this assertion, however. Warburton [15] questions whether those who suspect they are HIV positive would allow concerns about a future prosecution to have such an effect. Certainly some of those who suspect that they are HIV positive may well take what would seem to be the sensible course to prioritize their own health and seek the treatment that is now available. Indeed in Scotland, for the 4 months after Stephen Kelly’s conviction, there was a 16% increase in the rate of testing over the rate for the same 4 months the previous year, although it is not known whether there was a causal connection between the two events [16]. There will inevitably be others, however, who, through the fear of potential criminal liability, will be prepared to jeopardize their own health, particularly if they have other reasons to fear the law, have low self-worth, or already show a tendency to be in denial in relation to their HIV status. The only question is what proportion of those who suspect they are HIV positive will fall into this group.

Reduction in testing and disclosure due to increased stigma

Despite the progress made over the past 25 years, significant stigma still affects those living with HIV infection and AIDS (Orton, HIV related stigma; Department of Health update; http://www.keele.ac.uk/research/lpj/Law_HIVAIDSP project/MarchPresentations/KayOrton.ppt#1). By engaging the criminal law in the context of HIV infection, there is a risk of increasing the level of stigma attached to having HIV. The consequences of this could be dire for public health. Disclosure of status to others, including potential partners, could become even more difficult and less practised. Again, those who suspect they have HIV infection may not come forward for testing and those already diagnosed could, through fear of association with HIV-identifiable activity, not engage with HIV services. This in turn would lead to an increase in rates of infection, particularly in the undiagnosed pool of infection that the government is interested in reducing [2].

Few studies have focussed on the question of whether such prosecutions cause a general increase in stigma attached to HIV infection. One recent study [17] looked at the views of those living with HIV or AIDS on the criminalization of transmission. Although it could be argued that the single subject group limits the usefulness of this research, some of the results are nonetheless very interesting. Ninety per cent of those interviewed expressed some criticism of criminalization, with 20% citing as their primary concern the risk of increasing existing stigma.

Concern has also been expressed that prosecutions for HIV transmission have discriminated against certain ‘vulnerable’ groups. Three of the first cases in England involved immigrant men of black African origin. Whether or not these prosecutions amount to discrimination, it is certainly the case that the inevitable public association between these groups and HIV infection is an unfortunate consequence and may well serve to further negative stereotypes of such groups. The publicity may make the public more likely to think someone has HIV just because they belong to a potential risk group and subsequently to adopt inappropriate and discriminatory behaviour towards them.

Reduction in the use of postexposure prophylaxis

The risk of prosecution might stop the HIV-positive person from disclosing his or her status following unprotected sex and thus prevent the opportunity for the sexual partner to use postexposure prophylaxis.

The impact upon the patient–healthcare professional relationship

The patient’s right to confidentiality has always been a qualified right in the context of sexually transmitted infection and thus can, in rare circumstances, be breached in the public interest [18,19] (W v Egdell, 1990, Ch 359). In light of the recent prosecutions for HIV transmission, there has been increased interest amongst healthcare professionals as to the scope of their duties with regard to disclosure and a questioning of whether it is possible for a physician to be legally liable for the onward transmission of a disease [9]. In the United States in Tarasoff v Regents of the University of California [20], it was held that a psychotherapist whose client told him that he was going to murder a named person, and then did so, had a specific duty to warn the victim. For several reasons (principle and policy), it is thought unlikely that this duty to warn will be translated into English law [21].

Much concern nonetheless remains in medical quarters, and this was reflected in the creation of a recent draft briefing paper by The British HIV Association (Anderson et al., available at http://www.bhiva.org/) and in a recently sought declaration from the High Court in which the Health Protection Agency sought guidance from the court as to the duties of a physician with regard to disclosure of confidential information (including possible disclosure to the police) [22]. The case was based on an HIV-positive patient who, the clinic had reason to believe, was continuing to put others at risk of contracting HIV through unprotected sex. They were particularly concerned about the possibility of specific legal duties and obligations arising under the right to life in Article 2 and the right of privacy in Article 8 of the European Convention on Human Rights and what if anything the physician could or should do in this situation. Judge Munby concluded that it was not the role of the court...
to give speculative advisory opinions and so no help was gleaned from this case.

Those interested in public health are concerned that breaches of confidentiality, or concerns about this, may lead to a general distrust of the medical establishment. In the context of HIV infection, this would inevitably lead to reluctance in patients to engage with medical services and, in particular, to give information about their sexual contacts. The number harmed in the long term could far outweigh any alleged short-term ‘gain’ [23].

The Department of Health [24] has responded to these concerns about confidentiality in the context of HIV and other sexually transmitted infections and has produced a consultation document aimed at clarifying these issues.

Crown Prosecution Service consultation
The Crown Prosecution Service (CPS) [6] has produced a ‘draft policy for prosecuting cases involving sexual transmission of infections which cause grievous bodily harm’. This is a public consultation paper. The final report will be published in 2007. The purpose of this document is not to decide whether there should be prosecutions but to provide transparency and consistency of approach across the country and to identify what factors should be taken into account when deciding whether to proceed with prosecution in an individual case. There have been several criticisms of this report [25].

Conclusion
Whilst the CPS consultation process is extremely important and will hopefully produce a more coherent and consistent approach to these cases, the question of whether to change the law and prohibit prosecutions for reckless HIV transmission rests with the government.

Notwithstanding the moral culpability of knowingly putting others at risk, important public health concerns support the taking of an ‘exceptional’ course in this context and not prosecuting at all for reckless transmission of HIV infection. The issues giving rise to concern would benefit from further scrutiny best achieved by research into the impact of prosecution for reckless transmission on public health. If the concerns are shown to be justified, then this might form the basis of a successful campaign to change the law so as to prevent such prosecutions or alternatively, perhaps by compromise, to persuade the CPS to adopt a policy of prosecuting only in the most blameworthy cases, e.g. when there has been an explicit lie as to HIV status.

However this debate is finally resolved, what is not in doubt is that the need remains urgent to continue to provide health education in relation to HIV infection. One needs only to refer back to the case of R v Konzani, in which the 15-year-old complainant considered only the risk of other infection and of pregnancy from unprotected sex but did not consider the risk of HIV transmission, to know that such education remains essential if the ‘fight’ against the HIV virus is to be won.

Acknowledgement
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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 92).

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As the recent case of Health Protection Agency v X [2005] shows, these matters are not for the courts to give hypothetical guidance on. This Department of Health document aims to promote discussion and provide guidance around these difficult issues.

The resurgence of syphilis among men who have sex with men
Thomas A. Peterman and Bruce W. Furness

Purpose of review
To identify recent progress and emerging problems in addressing syphilis among men who have sex with men.

Recent findings
A resurgence of syphilis has occurred among men who have sex with men in many developed countries. Infection has been associated with HIV coinfection, multiple partners, and recreational drug use. Unlike HIV, oral sex appears to be a common route of syphilis transmission. Many prevention approaches have shown, at best, modest success. Variable clinical presentation and potentially inconclusive lab tests make diagnosis confusing.

Summary
As the infection remains relatively rare, clinicians treating men who have sex with men should maintain a high index of suspicion for syphilis lesions, and should screen their sexually active patients for latent disease. Debates about syphilis control and treatment continue. The clinical manifestations, serologic responses, efficacy of treatment, and complications of syphilis have always been complicated. HIV coinfection adds to the confusion.

Keywords
diagnosis, epidemiology, prevention, syphilis

Introduction
Nearly 12 million people per year acquire syphilis, mostly in Africa where congenital syphilis remains a major cause of stillbirth [1,2]. In many developed countries, syphilis reached the lowest levels ever recorded in the 1990s. From around 1999, however, small outbreaks were reported among men who have sex with men (MSM). These epidemics spread to populations in other areas and led to a resurgence of syphilis in many countries. Many of the MSM acquiring syphilis are coinfected with HIV. This confluence of epidemics brings with it new challenges for preventing syphilis and treating patients. During the past 2 years many papers have addressed these issues. Some describe advances in syphilis prevention or treatment while others are remarkable for their clarity in outlining the epidemiology or the longstanding clinical and prevention dilemmas that make syphilis such a fascinating disease [3,4**].

Epidemiology
Just as the incidence of syphilis in developed countries was reaching all-time low levels, reports began appearing of outbreaks among MSM [5*,6*]. These outbreaks were remarkable because sexually transmitted diseases had become relatively rare among MSM during the AIDS epidemic. Also remarkable was the rapidity with which the epidemics spread across widely separated areas in Europe, the United States, and Australia [6*]. In France, reported syphilis increased from 37 cases in 2000 to 428 in 2003; 96% of cases were male [7]. In the UK, cases of infectious syphilis increased from 293 in 1998, to 2226 in 2003, with a threefold increase in women and a 25-fold increase in MSM [8]. In Sydney infectious cases rose from six in 1999 to 162 in 2003; all were men [9]. In the United States, reported primary and secondary syphilis increased from 5979 in 2000 to 7980 in 2004; 84% of 7980 cases were male [10]. The epidemic was obvious in certain cities. In San Francisco, early syphilis cases increased from 44 in 1999 to 522 in 2003, 94% among MSM [11]. Other cities reported less obvious increases or even decreases, because decreasing rates in heterosexuals masked major increases in rates among the smaller groups of MSM. For example, in Chicago, between 1998 and 2002, reported primary and secondary syphilis cases remained fairly constant at 338 and 353 but during that time the number of cases decreased 68% among women and increased 400% among MSM [12].

The resurgence of syphilis suggested to some that advances in HIV therapy had led to a disinhibition of
behaviors among MSM who no longer feared AIDS. Reviews of behavioral studies found that there was no good evidence of disinhibition among individual MSM on highly active antiretroviral therapy (HAART); however, among all gay men, beliefs about the effectiveness of therapy were associated with unprotected sex [13]. Other studies suggested that the increased survival of high-risk HIV-infected MSM could lead to behavior changes in the population without changing the behavior of any of the individuals [14,15]. Biologic factors also suggest the syphilis epidemics could portend a worsening HIV epidemic because syphilis ulcers facilitate HIV transmission [16]. Syphilis may also accelerate progression of HIV-related diseases, though results are inconclusive. One study [17] found syphilis increased the viral load in 51 HIV infected men (mean 0.22 RNA log_{10} copies/ml) and decreased CD4 cell counts (mean 62 cells/mm³). A second study documented similar changes [18]. A third study found no statistically significant changes in 29 HIV-infected MSM with syphilis [19]. The impact of the syphilis epidemics on HIV incidence is difficult to measure. In San Francisco, HIV seroconversion was 14% per year among MSM acquiring syphilis, but the HIV incidence in the city did not appear to change between 1998 and 2002 [20].

Many of the MSM who acquired syphilis were surprised at their diagnosis because they had only had oral sex, and they did not think they could acquire syphilis via oral sex [12]. The fraction of syphilis transmission attributed to oral sex has been estimated at 20% among MSM in Chicago [12], 25% in Sidney [9], 37% in Brighton [21*], and 46% in Northern Ireland [21*].

In New York City, when 88 MSM with syphilis were compared with 176 MSM controls, the most important risk factor was having HIV infection [odds ratio (OR) 7.3] [22]. In the San Francisco STD clinic, compared with other MSM, the 53 men with syphilis were more likely to use methamphetamine and Viagra (Piller, New York, USA) (OR 6.2), have HIV infection (OR 3.9), have strong gay community affiliation (OR 2.3), and have recently met partners via the Internet (OR 2.1) [23]. A survey of MSM attending bars and clubs in 10 states found Viagra was used in the previous 3 months by 9% of HIV-uninfected men and 29% of HIV-infected men [24]. Among MSM in the Brighton, UK, genitourinary medicine clinic, syphilis was associated with having more oral sex partners (OR 2.1), receptive anal sex (OR 2.9), and unprotected receptive anal sex (OR 2.2) [25].

Public health approach
Public health interventions have been multifaceted [11,26]. Prevention efforts to control the epidemic have often included information campaigns aimed at informing MSM of the risk of syphilis. San Francisco launched the ‘Healthy Penis’ campaign centered on a giant penis that made appearances in ads and at pubic gatherings. Evaluation showed that 80% of 244 MSM sampled were aware of the campaign (33% mentioned it spontaneously), and those who spontaneously mentioned it were 3.2 times more likely to report being tested for syphilis in the previous 6 months [27*]. Other campaigns have included less explicit mascots, including a syphilis sore that resembles a walking raspberry, and various pictures of MSM [28]. In 2003 two episodes of the US TV show ‘ER’ contained a storyline about MSM diagnosed with syphilis. A subsequent Internet survey found those who had seen the program were more likely to have intentions to get screened for syphilis [29].

Sexual transmission of syphilis occurs only when lesions are present (though often unnoticed) during the primary or secondary stages. Serologic screening programs can prevent transmission if they identify and treat persons who would otherwise have lesions and transmit to others. Early (<1–2 years) latent syphilis may lapse or relapse into secondary syphilis, so treating primary, secondary, or early latent infections may reduce transmission. Treating later infections benefits the patient by preventing tertiary syphilis, but does not affect the incidence of syphilis in the community. Thus, evaluating screening programs requires information on the cost and benefits in terms of cases prevented (or, at least, early cases treated). Many papers report only the number tested and the percentage positive. A review of screening in seven areas across the United States found 132 early cases detected when 14 143 MSM were screened [30*]. Screening in nonmedical settings detected 0.2–5.0% of early syphilis reported among MSM in these areas, but the costs of the outreach testing were often not available. An excellent report from Australia detailed the cost of an outreach program in which 224 men were tested and five (2.2%) had newly diagnosed syphilis [31]. None of the infections were early (infectious) cases, and they were detected over the course of 6.5 years of screening by one nurse practitioner working 5 h per week at a total cost of €26 015. This high cost is not justified based on the number of cases found, but may be valued for raising awareness in the community at risk. In Brighton, UK, a 7-week campaign involving 26 venues tested 1090 MSM and found six with early syphilis, but the cost details were not reported [32]. In New York City, a variety of health services of special relevance to MSM were offered at special events in bars and clubs. Nine events over 6 months reached 1634 men but only 161 were tested for syphilis and two were newly diagnosed early cases. Though well received by the community, the events cost US$10 000 each and were thus not as cost-effective as other approaches to finding and treating syphilis [33].

Stand-alone screening programs are more expensive than screening during HIV clinic visits, when the cost is just
the cost of the test. Thus, screening has been emphasized for MSM in general, and especially for MSM who are being treated for HIV. Some clinicians, who are accustomed to higher yields of diagnostic testing, may resist screening because tests are rarely positive, but screening in the clinical setting would be cost-effective at yields well below 1%. Periodic screening of MSM who have risky sex partners has been recommended by the US Preventive Services Task Force [34]. An HIV clinic in London added syphilis serology to routine blood orders and detected 40 new infections among 2389 MSM tested in 2003 [35**]. In Sidney, guidelines recommended annual screening for MSM with at least one partner in the year for HIV, syphilis, hepatitis A and B, gonorrhea (rectal, urine, pharyngeal), and chlamydia (rectal and urine). Following these guidelines, testing increased for all of these infections, with complete series testing increasing from 46% in 2000 to 61% in 2002 [36**]. In San Francisco, screening at an HIV clinic identified 15 new syphilis infections and 60 new cases of chlamydia or gonorrhea (with 88% at nonurethral sites) out of 586 men tested [37]. Screening coverage has been estimated in San Francisco where 60% of 676 MSM attending sex clubs reported they had been tested for syphilis within the preceding 6 months; the goal for the health department was set at 90% [38].

Targeted mass treatment for syphilis was studied in Vancouver [39]. Treatment of 4384 at-risk residents with oral azithromycin resulted in a short decrease in syphilis rates followed by a rate rebound and a caution against routine mass treatment.

Partner notification – a traditional focus of syphilis control programs – appears to have been less successful in the current epidemic than in the past. A review of 18 studies from 1975 to 2004 found an average of one newly identified infected partner for every five index patients interviewed, though success appeared to be decreasing over time [40*]. Partner notification for MSM in 2003 found one newly infected partner for every 10 index patients interviewed [41]. Partner notification was difficult for several reasons: interviews were delayed when diagnoses were made outside of health department clinics; many partners were anonymous and could not be found; and some MSM and their healthcare providers did not trust the health department. As the Internet became an important way to meet partners, partner notification efforts expanded to the Internet to reach people known only by an e-mail address or a chat room name. Successful partner notification via the Internet has been reported, though the costs remain unclear [42].

Other Internet prevention approaches have been described, including banner ads for prevention web sites, web town hall meetings, and one-on-one interventions in chat rooms [43]. In San Francisco, banner ads cost US$1000–$10 000 per month. Nine banner ads made 33 million appearances generating 32 000 click-throughs to the health department web site. The most clicked-through ad was ‘Got a sore or rash?’ at 0.14%. Seven 1 h chats on Gay.com averaged 120 visitors and 15 questions answered per hour. Question/answer messages were also posted [44]. Residents of San Francisco could download a requisition for free syphilis serologic testing at participating commercial labs. In the first year, 218 tests were performed and six infections were newly identified. The cost of maintaining this service was US$40 per week plus US$31 per test [45].

In the past, patients with syphilis in the United States were usually treated in health department clinics. MSM with syphilis, though, are mostly seen by private practitioners. Thus health department prevention programs have worked on increasing awareness of private practitioners to look for and diagnose syphilitic lesions, screen for latent infections, talk to their patients about the risks of syphilis, and refer infected patients to the health department for partner notification [46]. Some health departments have stationed employees in private clinics that serve a large number of MSM so they can assist with counseling and follow-up like they previously did in health department clinics.

**Diagnosis and treatment**

Syphilis can manifest itself in many different ways and laboratory tests for confirmation may be inconclusive. Diagnosing syphilis has always been confusing, and it has become even more challenging as it has become rarer. Although many have suspected that the manifestations of syphilis are different in HIV-infected persons, large studies have not found significant differences [47–49]. Painless ulcers in the mouth, penis, or rectal area should suggest primary syphilis [50]. Serologic tests may be negative at this stage, and dark field exams are rarely available, so diagnosis and treatment should be based on clinical suspicion (Table 1) [51]. Secondary syphilis often appears as a symmetric generalized rash that may involve the palms and soles, and often includes highly infectious

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary Sensitivity (%)</th>
<th>Secondary Sensitivity (%)</th>
<th>Latent Sensitivity (%)</th>
<th>Tertiary Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontreponemal tests</td>
<td>78–86</td>
<td>100</td>
<td>95–98</td>
<td>71–73</td>
<td>97–99</td>
</tr>
<tr>
<td>Treponemal tests</td>
<td>76–84</td>
<td>100</td>
<td>97–100</td>
<td>94–96</td>
<td>97–99</td>
</tr>
</tbody>
</table>

Nontreponemal tests include venereal disease research laboratory (VDRL), rapid plasma regain (RPR), unheated serum regain (USR), reagin screen test (RST), toluidine red unheated serum test (TRUST). Treponemal tests include fluorescent treponemal antibody-absorption (FTA-ABS), microhemagglutination assay for antibodies to Treponema pallidum (MHA-TP), FTA-ABS double staining. Source: Larsen et al. [51].
mucous membrane lesions [50,52]. Serologic tests are almost always positive in secondary syphilis (especially if serum has been diluted to avoid the prozone effect) [51], though treatment might be given without waiting for laboratory confirmation if clinical suspicion is high.

Latent syphilis is a serologic diagnosis based on a combination of treponemal tests, nontreponemal tests, and past history [51]. Screening in the United States has traditionally started with a nontreponemal test followed by a treponemal test for those who initially test positive. In many other countries, screening has started with a treponemal test with nontreponemal tests used for confirmation [53]. Automated treponemal enzyme immunoassay screening is now being introduced into many areas necessitating new algorithms for interpreting results [54]. The sensitivity of nontreponemal tests is low if syphilis has been latent for many years, so it may be difficult to conclude with certainty that a patient with a positive treponemal test and negative nontreponemal test is uninfected [51,53]. As syphilis becomes increasingly uncommon, however, even with a test specificity of 99%, there will be more false positives than true positives in most settings. Serologic tests may remain positive following successful treatment of latent infections, so subsequent latent infections are diagnosed when there is a fourfold or greater increase in the titer of a nontreponemal test. Health departments maintain records of past positive syphilis tests to assist in interpretation of subsequent positive tests.

Neurosyphilis can appear as an early or late manifestation. Late neurosyphilis has become rare, possibly because antibiotic treatment for other conditions is sufficient to halt progression to neurosyphilis. Prompt diagnosis requires a high index of suspicion for syphilis when MSM present with ocular, meningeal, or cranial nerve findings [55].

The potential for neurosyphilis also raises the issue of the need to do lumbar punctures in patients with syphilis to see if they may have ‘asymptomatic neurosyphilis’. This is a confusing diagnosis because it has long been known that patients with early syphilis may have treponemes in their cerebrospinal fluid (CSF); and treatment regimens for early syphilis are insufficient to kill treponemes in the CSF; yet, for some reason, treatment of early syphilis apparently prevents progression to neurosyphilis [48,56]. There continues to be debate about whether or not coexisting HIV infection may increase the risk of asymptomatic neurosyphilis. Many persons with early syphilis will have CSF abnormalities (if they are looked for) and the criteria for doing lumbar punctures in asymptomatic persons are debated [48,49,55]. The Centers for Disease Control and Prevention (CDC) recommend lumbar puncture for all HIV-infected patients with late latent syphilis and acknowledges that some specialists recommend lumbar puncture more broadly [57**].

Treatment for syphilis remains unchanged: benzathine penicillin G 2.4 million units intramuscularly, one dose for early syphilis, three doses (each a week apart) for late syphilis [57**]. Alternative approaches vary slightly in different countries [56]. Some experts recommend treating all syphilis in HIV-infected patients with three doses of benzathine penicillin G. Nontreponemal test titers should be assessed regularly over the following 1–2 years to assure adequate response to therapy (a fourfold or greater decrease in titer) [57**]. Azithromycin looked like an effective oral regimen in one clinical trial [58], but problems with resistance limit the usefulness [59]. There continues to be confusion between Bicillin L-A (King Pharmaceuticals Inc., Bristol, Tennessee, USA), which is used to treat syphilis, and Bicillin C-R, which contains only half the dose of benzathine penicillin G, and may thus not be sufficient to cure syphilis [60]. This confusion was partly because packaging was similar, and partly because both are called Bicillin. The manufacturer has made changes to the packaging, which may reduce some errors.

**Conclusion**

One of the oldest known diseases continues to teach us new things. Modern technologies have helped spread syphilis; the Internet has facilitated recruitment of sex partners and international travel has facilitated contacts in distant areas. Modern technologies may also contribute to syphilis control. The Internet allows new opportunities for partner tracing and public education. Advances in diagnostics may allow testing of oral fluid [61], rapid fingerstick testing [62,63], or new automated tests [64]. The entire genome of Treponema pallidum has been sequenced. It is hoped that identification of molecules on the surface of T. pallidum will lead to the development of effective multivalent vaccine [4**]. There is still no magic bullet [65]; the search, however, continues!

**Acknowledgements**

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 107).


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Risk selection and targeted interventions in community-based control of chlamydia
Jan Hendrik Richardusa,b and Hannelore M. Götz a,b

Purpose of review
To describe recent developments in the community-based approach of high-risk groups for Chlamydia trachomatis infection, and to discuss the assessment of impact of selective systematic screening on the transmission of C. trachomatis in the community.

Recent findings
Two large home-based screening programs in Europe have recently shown that systematic postal screening for C. trachomatis infection is feasible, but certain high-risk groups are poor participants. This underscores the need for risk selection and targeted approaches. A prediction rule has been developed which can assist in identifying high-risk groups and can be used as a tool for (self) selection for screening. The Internet has been shown to be a promising medium to promote chlamydia testing. School-based programs also succeed in including high-risk groups in screening programs. Recently developed dynamic simulation models, which take into account transmission of C. trachomatis, can assist in the development and evaluation of targeted screening strategies.

Summary
Chlamydia will not likely be controlled by one standard approach. Risk selection strategies need further development and different systematic approaches at the community level, including postal screening, school-based screening, and the Internet may produce the desired public health effect of decreasing morbidity and reducing the transmission of C. trachomatis in the community.

Keywords
Chlamydia trachomatis, high-risk group, prediction rule, screening, transmission modelling

Introduction
Chlamydia trachomatis infection is the most prevalent sexually transmitted bacterial infection. It is usually asymptomatic and persistent in nature, and is distributed widely in the population, particularly in young people. The prevalence of chlamydial infection has increased recently in many countries [1]. In women, chlamydial infections are a major cause of pelvic inflammatory disease (PID), ectopic pregnancy, tubal infertility and chronic abdominal pain [2]. Chlamydial infections in men also cause urogenital diseases and possibly infertility [3].

The high prevalence of C. trachomatis infection and the seriousness of its complications have led to the development of screening programs to detect and treat chlamydia. The introduction of nucleic acid amplification tests (NAATs) for detection of chlamydia, which can be performed using urine, vaginal or cervical specimens, have made it possible for patients to avoid clinics and invasive examinations [4]. Two distinct approaches to chlamydia screening exist: opportunistic and systematic. Opportunistic screening involves offering tests to people already attending a health service for another reason. Systematic screening involves actively inviting the target population to be tested. Both methods can be universal or selective in their targeting of participants. Universal opportunistic screening can be achieved by involving the general practitioner (GP) in countries with mandatory registration of the population with a GP. Examples of opportunistic selective screening are programs based in special healthcare settings such as family planning and youth clinics. Systematic universal screening of the general population can be organized by healthcare organizations issuing invitations. Within systematic screening a risk selection can be made on the basis of risk factors, thus aiming to include only those at high risk of infection.

Any screening program should reduce morbidity or mortality. As chlamydia is an infectious disease, screening should also reduce transmission and thereby the prevalence of chlamydial infections in the population [5,6]. There is evidence that systematic screening can reduce the incidence of PID in women by about half after 1 year of screening. This evidence is applicable to women aged 18–34 years at high risk of chlamydia who are invited to attend health facilities for screening [7], and to final year school students screened using home-collected specimens [8]. Opportunistic chlamydia screening has not been evaluated in a randomized controlled
trial and Low et al. [9,10] point out the inherent difficulties of attaining and sustaining adequate coverage using opportunistic screening. Finally, no trial has investigated the effects of screening on chlamydia transmission [9]. In Sweden, where opportunistic screening and mandatory partner notification for chlamydia have been in effect since the 1980s, the chlamydia rates doubled between 1997 and 2003 to prescreening levels [11]. In the USA the current (opportunistic) screening program appears unable to bring about and sustain a reduction in the risk of acquiring chlamydia [12].

The National Institute for Health and Clinical Excellence (NICE) in the UK is preparing a comprehensive rapid review of evidence for the effectiveness of screening for genital chlamydial infection in sexually active young women and men (http://www.nice.org.uk). The purpose of this article is to describe recent (January 2005–August 2006) developments in the community-based approach to screening high-risk groups for C. trachomatis infection, and to discuss the impact of selective systematic screening programs on the transmission of C. trachomatis in the community.

**Systematic postal screening for Chlamydia trachomatis**

In 2005, the results of two large-scale systematic postal screening projects were published following an earlier study in Denmark [13]. The chlamydia screening studies (ClaSS) were conducted in the UK and included 19773 men and women aged 16–39 years [14,15*]. The study design was a cross-sectional survey of people randomly selected from general practice registers. Participants were invited to collect their own specimens and return them by mail, and to complete a questionnaire on risk factors. NAATs were used to detect C. trachomatis. Uptake in 16–24-year-olds was 31.5% and was lower in men, younger adults, and those living in disadvantaged areas. The overall prevalence of chlamydia was 2.8% in men and 3.6% in women, but it was higher in people younger than 25 years (men 5.1%; women 6.2%). Prevalence was higher in the subgroup of younger women who were harder to engage in screening. The strongest determinant of chlamydial infection was having one or more new sexual partners in the past year. The authors concluded that postal chlamydia screening was feasible, but coverage was incomplete and uptake modest. Lower coverage of postal screening in areas with more nonwhite residents along with poorer uptake in more deprived areas and among women at higher risk of infection could mean that screening leads to wider inequalities in sexual health.

The PILOT C. trachomatis study was conducted in the Netherlands and included 21 000 men and women aged 15–29 years [16**,17]. The study design was a stratified national probability survey according to area density, with participants randomly selected in four regions from the civil registration of the municipalities involved. Participants were invited to collect their own specimens and return them by mail, and to complete a questionnaire on risk factors. NAATs were used to detect C. trachomatis. In total 41% (8383) responded by sending in urine along with the questionnaire, and 11% (2227) returned a refusal card. Nonresponders included both higher and lower risk categories. Chlamydia prevalence was significantly lower in rural areas (0.6%) compared with very highly urbanized areas (3.2%). Overall prevalence was 2.0% (women 2.5%; men 1.5%). Infection was associated with high urbanization, low education and minority ethnic groups, while participation among those with these characteristics was low. The authors concluded that in this large, population-based study there was a very low prevalence in rural populations, suggesting that nationwide systematic screening is not indicated in the Netherlands and that targeted approaches are a better option.

Both the ClaSS and PILOT C. trachomatis projects have published additional studies focusing on the management of chlamydia cases and their partners [18], partner notification [19*], and on the experience [20], anxiety levels [21], and acceptability and consequences [22] in those screened.

The projects in the UK and the Netherlands show that systematic postal screening is feasible in terms of program organization, and generally acceptable to the target population. Certain groups, however, were difficult to engage in screening. The (partial) exclusion of highly prevalent groups jeopardizes the effect of systematic screening in terms of impact on the transmission of C. trachomatis in the population, as well as contributing to sexual health inequalities. Also, systematic universal screening is not likely to be cost-effective in a population with relatively low chlamydia prevalence. It is therefore crucial to develop effective strategies for selective screening by defining and targeting high-risk groups in order to increase their participation in screening programs for chlamydia.

**A prediction rule for estimating the risk of chlamydial infection**

Selective screening, incorporating risk assessment, may increase the cost-effectiveness and results in fewer individuals undergoing an unnecessary test. This approach, however, may lead to an unacceptably high proportion of missed infections. Selective screening criteria for women have been applied in various clinic-based, opportunistic chlamydia screening programs, but their effectiveness has not been firmly established [23,24]. Selection criteria for both sexes have been studied in population-based screening programs, but these have not led to practical guidelines for selection [25,26]. In the PILOT C. trachomatis project in the Netherlands behavioural, clinical, and geographic risk
factors in 15–29-year-old women and men were identified from which a prediction rule for *C. trachomatis* infection was developed [27**].

Independent risk factors identified in the PILOT *C. trachomatis* project were number of lifetime sex partners, recent partner change, high urbanization, young age group, Surinamese/Antillean ethnicity, low and intermediate education, symptoms (for women, postcoital bleeding; for men, frequent urination), and no condom use during last sexual contact. For each characteristic, a score was calculated based on the regression coefficients, with rounding to simplify the calculation. For each individual, these scores were added into a sum score, reflecting the probability of chlamydial infection. This prediction rule can be used for selection in chlamydia screening. Table 1 shows the results for different cut-off levels of sum scores. The first row gives the scenario for performing screening in the whole study population and therefore identifying all infected patients (sensitivity 100%). When screening is performed in all sexually active participants with a sum score of at least 8, the number to be screened in the PILOT *C. trachomatis* population would be reduced to 33%. Twenty-one percent of the cases, however, would then be missed (sensitivity 79%). The expected chlamydia prevalence in the screened group would be 5.7%, in contrast to 2.3% on average.

The prediction model with the data from the PILOT *C. trachomatis* project showed adequate discriminative ability at internal validation. External validation of the prediction rule with data from other studies in the Netherlands gave reasonable results [28*]. Although further validation is necessary when applying the prediction rule to other countries, this methodology opens new avenues for risk assessment in community-based screening and possibly in opportunistic screening as well. In community-based screening this approach could be applied to motivate high-risk individuals with a score above a certain level to participate, or as a tool for self selection when screening in areas with low *C. trachomatis* prevalence. For instance, an invitation letter for screening could include a simple questionnaire for calculating a personal score, together with a request form for a test kit. In opportunistic screening, the clinician can ask the patient questions relating to the predictive criteria.

### Novel interventions for chlamydia screening targeting high-risk groups

When the prediction rule is used to identify high-risk groups and possibly as a tool for health education and (self) selection for *C. trachomatis* screening, innovative interventions are needed to actually reach out and encourage high-risk groups to participate in a screening program. The literature on *C. trachomatis* testing outside the clinical setting has been reviewed by Ford et al. [29]. The major challenge of such targeted interventions is that they have a direct impact on decreasing rates of infection in the community.

Recently, the Internet has been investigated as a possible tool to promote chlamydia testing. An Internet-based self-selective testing approach by means of home sampling in the general population was introduced in a Swedish county [30*]. It was found that simplifying and increasing the accessibility of chlamydia testing by means of the Internet and home sampling proved feasible. In addition, self-risk assessment was found to improve the chances of finding people infected by *C. trachomatis*, especially men, if an accessible testing method is offered.

The authors concluded that this new method can be used in conjunction with regular preventive methods and may encourage young people to be tested.

An educational Internet-based program for women to facilitate home screening for *C. trachomatis* was also introduced in the United States [31*]. The authors concluded that women will use the Internet to request and use home sampling kits for chlamydia. High prevalence was detected and questionnaires indicated high-risk sexual behaviour. This study found that only 29% of the kit users had received a pelvic examination within the previous year, supporting the hypothesis that the Internet screening method may reach a group of high-risk women not accessing traditional healthcare.

### Table 1 Implications of using the prediction rule for screening for *Chlamydia trachomatis*

<table>
<thead>
<tr>
<th>Cut-off sum score¹</th>
<th>Sensitivity² (%)</th>
<th>Specificity³ (%)</th>
<th>Fraction positive⁴ (%)</th>
<th>PPV⁵ (%)</th>
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<td>3.7</td>
<td>17.5</td>
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<td>≥12</td>
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<td>≥13</td>
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<td>≥14</td>
<td>1.4</td>
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¹ Cut-off sum score: selection criterion for screening.
² Sensitivity: the percentage of detected chlamydial infections among our study participants when screening under the given selection criteria.
³ Specificity: percentage of chlamydia negative participants who would not be screened justify.
⁴ Fraction positive: percentage of the total population that is eligible for screening under the given selection.
⁵ PPV: prevalence in the screened population (predictive value of selection criterion).
C. trachomatis testing was offered to students at a vocational training school in the inner city with a high proportion of ethnic minorities, of which 24.5% proved to be positive for C. trachomatis [32*]. A high acceptance rate of chlamydia testing was found in both men and women of non-Dutch ethnicity. The authors concluded that high-risk individuals were accessed and that outreach testing at vocational training schools is feasible and efficient. Considering that approximately 40,000 students attend vocational training schools in Rotterdam, representing all ethnic groups, school screening may have an impact on the community prevalence of C. trachomatis infections.

In Philadelphia, USA, the C. trachomatis prevalence rate in 19,394 public high-school students aged 12–20 years was 8.1% among females and 2.5% among males [33*]. These authors also concluded that the effectiveness of a school-based screening program was demonstrated which identified and treated C. trachomatis and Neisseria gonorrhoeae infections. This approach may also lead to the identification and treatment of STDs that could otherwise go undetected. They also expressed the hope that large school-based programs will decrease the prevalence of C. trachomatis in the community.

Finally, another study in the USA assessed the trends and risk factors of chlamydial infections in thousands of young men and women entering a National Job Training Program [34,35]. The authors concluded that chlamydial infection is highly prevalent among socioeconomically disadvantaged young men and women and that young people entering the Program represent an important population for screening, possibly leading to successful reduction of chlamydia in the community.

Modelling and evaluating chlamydia screening

The hope expressed by those conducting Internet, school-based or other innovative selective screening programs is that these will contribute to a decrease in C. trachomatis transmission in the community. Mathematical models are important in supporting the development and evaluation of screening programs. Based on available epidemiological data, models assist in calculating the effects and costs of existing or proposed screening scenarios. Recently, a systematic review was published of the economic evaluations and modelling of screening for C. trachomatis up to mid 2004 [36*]. Most studies found chlamydia screening to be helpful, partner notification to be an effective adjunct, and testing with NAATs and treatment with azithromycin to be cost-effective. Methodological problems limit the validity of these findings: most studies used static models that are inappropriate for infectious diseases; restricted outcomes were used as a basis for policy recommendations; and high estimates of the probability of Chlamydia-associated complications may have overestimated cost-effectiveness. The authors concluded that the inappropriate use of static models to study interventions to prevent an infectious disease means that uncertainty remains about whether chlamydia screening programs are cost-effective or not. This view was shared by Welte et al. [37*].

By August 2006 two new studies [38*,39*] were published applying dynamic models to population-based C. trachomatis screening programs, both using home sampling approaches. One study from Denmark [38*] predicted costs, effectiveness and disease control. The other study [39*] estimated the cost-effectiveness of the systematic (one-off) PILOT C. trachomatis study in the Netherlands. Interestingly, the Dutch study shows that the one-off screening program reduces C. trachomatis prevalence in the whole population from 1.79 to 1.05%, after which it takes a long time to reach the steady state prevalence again. A similar, but less dramatic, finding was reported in the Danish study. This study started with a baseline prevalence of 4%. Home-based screening with home-based partner notification reduced the estimated prevalence to 2% after 3 years and reached 1% after 10 years of screening.

Dynamic modelling in C. trachomatis control is relatively new and the results are still rather tentative. As the models become more robust, taking into account the differences in population structures, sexual behaviour and healthcare systems as well as improved epidemiological data regarding complications of C. trachomatis infection, its effectiveness as a tool for developing and evaluating screening scenarios will improve. The findings of the above dynamic modelling studies clearly underline the need to identify and target high-risk groups for selective screening, because universal systematic screening will not always be feasible, either from the beginning in low prevalence countries, or after a number of years of screening in countries with an initial high prevalence.

Conclusion

The available evidence indicates that systematic community-based screening for chlamydia, in particular in women, is preferred over opportunistic screening. Universal systematic screening, however, does not appear feasible. The prevalence of C. trachomatis infection in the general population is too low in many countries to make this approach cost-effective. In addition, high-risk groups are not being reached, jeopardizing the impact of the screening program on the transmission of C. trachomatis in the community. Strategies need to be developed, therefore, for selective screening. The prediction rule will help define high-risk groups more clearly and can be used as a tool for (self) selection for screening. Internet and school-based programs are promising tools in reaching high-risk groups systematically and including them in screening.
programs. Advances have been made in the past 2 years in developing dynamic mathematical simulation models. These should be applied more intensively in future to assist the development and evaluation of new screening approaches, with particular focus on high-risk groups.

It is unlikely that chlamydia will ever be controlled by one standard approach. Different systematic approaches at the community level, including postal screening, school-based screening and the Internet, may need to exist along side each other, depending on the target group, to produce the desired public health effect. It may even be necessary to combine systematic screening with opportunistic screening in primary care to reach young men [40]. The challenge in the coming years will be to clearly identify and reach out to high-risk groups, and to establish the effectiveness of C. trachomatis interventions targeting these people.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 108–107).


An extensive and comprehensive report of the main findings of the CiaSS project in the UK. This is a study on systematic postal screening of CT, including nearly 20,000 participants.


This paper describes the main results of the PILOT C. trachomatis project in the Netherlands, together with the CiaSS project – the other recent large-scale study in Europe of systematic postal screening of C. trachomatis. The two studies are complementary, due to variations in the methods used and results obtained.


This paper describes a randomized controlled trial evaluating the effectiveness of practice-based partner notification by trained nurses.


This innovative study applies the methodology of prediction rules, increasingly used in clinical decision making, to a public health intervention. It is a promising new approach to support risk selection in chlamydia screening strategies.


This paper provides external validation of a prediction rule for risk of chlamydia infection and thereby strengthens its potential application for selective C. trachomatis screening.


This paper is the first to describe the application of the Internet in support of population-based C. trachomatis testing.


This paper shows that a group of high-risk women are accessed through the Internet for C. trachomatis testing who have not been reached via traditional healthcare.


This paper shows that outreach testing in school and group settings is highly efficient in comparison with street settings.
33 Asbel LE, Newbern EC, Salmon M, et al. School-based screening for Chlamydia trachomatis and Neisseria gonorrhoeae among Philadelphia public high school students. Sex Transm Dis 2006; 33:614–620. This paper describes the results of an extensive school-based screening program for C. trachomatis among high-school students in the USA.


Male circumcision as a preventive measure against HIV and other sexually transmitted diseases
Helen A. Weiss

Purpose of review
In 2005, 4.1 million people were infected with HIV. There is an urgent need to intensify and expand HIV prevention methods. Male circumcision is one of several potential approaches. This review summarizes recent evidence for the potential of male circumcision to prevent HIV and other sexually transmitted infections.

Recent findings
The first randomized controlled trial of adult male circumcision found a highly significant 60% reduction in HIV incidence among men in the intervention arm. Modelling this effect predicts that widespread implementation of male circumcision could avert 2 million HIV infections over the next decade in sub-Saharan Africa. The biological rationale is that the foreskin increases risk of HIV infection due to the high density of HIV target cells and lack of keratinization of the inner mucosal surface.

Summary
There is strong evidence that male circumcision reduces risk of HIV, syphilis and chancroid. If results are confirmed by two ongoing trials in sub-Saharan Africa, provision of safe male circumcision could be added to HIV prevention packages in high-incidence settings. This would also provide an opportunity for HIV-prevention education and counselling to young men at high risk of infection.

Keywords
HIV, male circumcision, sexually transmitted infections

Introduction
In 2005, 4.1 million people were newly infected with HIV, mostly through heterosexual intercourse [1]. This alarming number of infections highlights the urgent need to intensify and expand proven prevention methods, and further, to identify and implement new methods of HIV prevention. Male circumcision, one of the most common surgical procedures globally, is a potential new HIV prevention method, along with vaginal microbicides, pre-exposure prophylaxis with antiretrovirals, herpes suppressive therapy and HIV vaccines [2–4]. This paper reviews the recent evidence for a protective effect of male circumcision against HIV and other sexually transmitted infections (STIs).

Male circumcision and HIV infection
Systematic reviews of observational studies provide compelling evidence that circumcised men are at lower risk of HIV [5,6]. The studies show a strong and consistent protective effect of male circumcision on HIV infection after adjustment for potential confounders [adjusted risk ratio (RR) = 0.56, 95% confidence interval (CI) 0.44–0.70 in general populations; adjusted RR = 0.29, CI 0.20–0.41 in high-risk populations] [5]. Observational studies are inherently limited by potential selection biases, however, and study quality was variable [6]. To overcome these limitations, three randomized controlled trials (RCTs) of circumcision among consenting, healthy adult men in Uganda, Kenya and South Africa started in 2002–2003. In each trial, men were randomly assigned to receive circumcision immediately or to wait until the end of the trial, and were followed to assess HIV incidence. A further trial in Rakai, Uganda, is evaluating the impact of male circumcision on male–female HIV transmission.

Randomized controlled trial of adult male circumcision in Orange Farm, South Africa
Results of the RCT in the Orange Farm area in South Africa were published in 2005 [7]. In this trial, 3128 HIV-negative men aged 18–24 years were randomized to immediate or delayed circumcision. Men in both arms received individual counselling on sexually transmitted disease (STD)/HIV prevention at each visit, and were encouraged to attend voluntary counselling and testing, including access to antiretroviral therapy when it became nationally available in 2004. The trial was stopped following a recommendation by the Data and Safety Monitoring Board when interim analyses found men in the intervention arm at strongly reduced risk of HIV infection (rate ratio = 0.40, CI 0.24–0.68; P<0.0001). The estimated
A protective effect was even stronger (rate ratio = 0.24, CI 0.14–0.44) when data were re-analysed by actual circumcision status (i.e., allowing for men randomized to be circumcised but who chose not to be, or vice versa). The effect size in this trial is similar to that in previous cohort studies (Fig. 1) [7**,8–11], which are generally less susceptible to bias than cross-sectional studies.

**Potential impact and cost-effectiveness of male circumcision on HIV spread in Africa**

Based on the effect estimate found in the RCT, full coverage of male circumcision in sub-Saharan Africa would avert an estimated 2.0 (1.1–3.8) million new HIV infections and 0.3 (0.1–0.5) million deaths over the next 10 years [12**]. This means that male circumcision would be equivalent to an intervention (such as a vaccine or increased condom use) that reduces transmission in both directions by 37%. As expected, the impact would be greatest where there is highest HIV incidence and lowest rates of circumcision, and would be even more dramatic if (as must be the case) male circumcision were combined with other prevention strategies.

Preliminary calculations indicate that the cost-effectiveness of male circumcision for HIV prevention in sub-Saharan Africa compares favourably with other interventions such as improved STD treatment and school-based educational interventions [13]. Based on the South African data, each 1000 adult circumcisions in that population would avert an estimated 308 HIV infections in men and women over 20 years, at a cost of $181 (95% CI $117–306) per HIV infection averted [14]. Although these calculations incorporated costs of the procedure and treatment of adverse events, training or health infrastructure improvements were not included, and further work is needed in this area.

**Recent observational evidence on male circumcision and HIV**

Two recent longitudinal studies have provided additional observational data on the association of male circumcision and HIV incidence. One, a study of HIV acquisition among 745 Kenyan truck drivers [15**], estimated female–male HIV transmission probabilities per coital act. This study estimated HIV-1 infectivity taking into account multiple concurrent partnerships of different types. Overall infectivity was significantly higher for uncircumcised than for circumcised men (1.28% compared with 0.51% risk per contact; $P = 0.04$). Lack of circumcision significantly affected risk of HIV transmission in men at high risk, such as those with genital ulcer disease during follow-up (infectivity ratio 4.3, $P = 0.04$). This evidence of a stronger protective effect of circumcision among higher risk men is consistent with results from previous observational studies [5,6**], and may be due to an indirect effect through protection against other STIs [16**].

The major strength of this study is the prospectively collected sexual behaviour data, which minimize reporting bias, and the data on concurrent partnerships, which allows estimation to be closer to HIV transmission.
patterns in populations than those from studies of HIV-1 serodiscordant couples. Notably, the estimated rate in uncircumcised men is substantially higher than the female–male transmission rate per sexual contact estimated from discordant couples in Uganda (0.13%) [17] but is lower than the estimated rate among young male military conscripts in Thailand (5.96%) [18]. A limitation of the study was that HIV-1 infection status and disease status of sex partners was unknown and is likely to affect infectivity as transmission probabilities are higher during acute HIV infection [19].

A second prospective study of male circumcision and HIV incidence has added to the sparse literature on the impact of circumcision among men who have sex with men (MSM) [20]. The study, of 3257 high-risk MSM in six US cities enrolled from 1995–1997, found that lack of circumcision was associated with twice the risk of HIV seroconversion after adjusting for socioeconomic and recent sexual behavioural variables [odds ratio (OR) = 2.0, CI 1.1–3.7]. These findings are similar to those of a previous study among MSM [21] (OR = 2.0, CI 1.0–4.0). Biologically, less protection might be expected among men practising insertive, rather than receptive, anal intercourse, but a study of 63 recently infected HIV positive MSM in Australia found no evidence of this [22].

Male circumcision is now included in Demographic and Health Surveys (DHS), and analysis of the association with HIV using DHS data and AIDS Indicator Surveys in seven sub-Saharan African countries found a significant association in one country only (Tanzania) [23]. In contrast, the earlier systematic review found a significant protective effect in six out of nine population-based cross-sectional studies that adjusted for confounding [6]. The inherent limitations of cross-sectional studies may contribute to this discrepancy [6]. For example, men may become infected before being circumcised, especially in countries where the median age of circumcision is in the late teens or later, such as in South Africa [24], Lesotho [25] and Tanzania [26]. Further, important differences in behaviour between circumcised and uncircumcised men are unlikely to be sufficiently adjusted for in these studies, especially in countries where circumcision is the norm, such as Burkina Faso, Cameroon and Ghana, and finally, misclassification of self-reported circumcision status [27,28] is likely to underestimate any association.

Male circumcision was significantly associated with lower HIV prevalence (and lower cervical cancer incidence) after adjusting for religion in a recent ecological analysis of 118 developing countries in sub-Saharan Africa [29]. This evidence is strengthened by the finding that male circumcision was strongly associated with lower HIV prevalence among countries with primarily sexual HIV transmission (P<0.001), but not among countries with primarily nonsexual HIV transmission (P = 0.77).

**Biological rationale for increased risk of infection**

For men acquiring HIV heterosexually, the virus enters through the penis, and several factors will influence risk of acquisition, including the type, density and distribution of HIV-1 target cells in the penis, and the degree of keratinization of the epithelium [30].

Unlike the glans penis and the outer surface of the foreskin, the inner mucosal surface of the foreskin is thinly keratinized [31], and hence susceptible to minor trauma and abrasions which facilitate entry of pathogens (both bacterial and viral) [32]. Also, the preputial sac under the foreskin may provide a warm, moist environment to enable pathogens to replicate, especially when hygiene is poor [33].

The foreskin may also increase risk of HIV infection specifically as tissue from the inner surface of the foreskin mucosa contained higher proportions of HIV-1 target cells than cervical tissue [34]. Further, a recent study showed that the density of HIV-1 target cells in the inner foreskin was similar to that in the glans penis and outer foreskin, but those in the inner foreskin were closer to the epithelial surface than those situated elsewhere in the penis, due to the lack of keratin [31]. In an uncircumcised man, the cells in the inner foreskin and frenulum are directly exposed to vaginal secretions during heterosexual intercourse, and this superficial location of the HIV-1 target cells presumably increases risk of infection (Fig. 2). In contrast, in circumcised men, the penile shaft is thought to be covered with a thickly keratinized epithelium, providing some protection from infection [31]. A study of distribution of HIV-1 target cells among foreskins of 39 men circumcised in Kisumu, Kenya during the RCT [30] found that Langerhans cells were more likely to be found near the surface of the epithelium than other cells, again potentially increasing risk of HIV-1 infection in uncircumcised men. Perhaps the most direct evidence of the susceptibility of the foreskin to HIV-1 infection comes from Patterson et al. [34] who infected foreskin biopsies *ex vivo* with HIV-1 in explant culture, and found that infectivity of the inner mucosal surface was several times greater than that of cervical tissue, which is a known site of HIV-1 acquisition in women.

**Male circumcision, genital hygiene and HIV infection**

The role of genital hygiene in the association between male circumcision and HIV infection is unclear [35,36]. One recent study of 386 uncircumcised men attending an STD clinic in Durban, South Africa, defined subpreputial penile wetness as a marker of poor penile hygiene, and
found a significant association between this and HIV infection (OR = 2.38, CI 1.43–3.97). Subpreputial penile wetness itself was associated with lower socio-economic status, more lifetime sexual partners, and not washing after sex [37]. Another cross-sectional study, of 150 male partners of women with lower genital tract symptoms from a family planning clinic and an STD clinic in Nairobi, Kenya, also found that increased postcoital washing was associated with lower HIV infection. Male circumcision was significantly associated with lower risk of HIV in this study (OR = 0.12, CI 0.02–0.72) in addition to being associated with superior genital hygiene.

**Male circumcision and ulcerative sexually transmitted infection**

The impact of male circumcision on HIV will also be affected by any impact on other STIs, which are themselves co-factors for HIV transmission. The first systematic review and meta-analysis of the association of male circumcision with ulcerative STDs (syphilis, chancroid and genital herpes) was recently published [16**]. Twenty-six articles met the inclusion criteria for the review. Most syphilis studies reported a substantially reduced risk among circumcised men (summary RR = 0.67, 95% CI 0.54–0.83), although there was significant between-study heterogeneity (P = 0.01). There was also strong evidence of a reduced risk of chancroid in circumcised men but, in contrast, only weak evidence of an association with HSV2 infection (summary RR = 0.88, 95% CI 0.77–1.01). The results suggest that potential male circumcision interventions to reduce HIV in high-risk populations may provide additional benefit by protecting against some other STIs.

These data are supported by recently published data from the 2001 Botswana AIDS Impact Survey [39]. In this large nationally representative study, 17% of men reported being circumcised, and were significantly less likely to report recent urethral discharge or genital ulcer (adjusted OR = 0.61, CI 0.57–0.66). The size of this study enables precise estimates of effect, but conclusions about the impact of circumcision on STDs are limited because of the reliance on self-reported STDs and the joint outcome of urethral discharge and genital ulcer, rather than analyses of these separately.

**Male circumcision and Chlamydia trachomatis**

*Chlamydia trachomatis* is the most common bacterial STD, with an estimated 89 million new cases of genital chlamydial infection annually [40]. Recent evidence for a protective effect of male circumcision with *C. trachomatis* infection in women comes from a large, multicentre case–control study of invasive cervical cancer [41]. The study was located in five sites (Colombia, Spain, Brazil, Thailand and the Philippines) and participants were 1029 female controls with a stable male partner. Circumcision is the cultural norm in the Philippines (prevalence of 92.5% in this study) but uncommon in the study populations from the other countries. Overall, *C. trachomatis* seroprevalence was significantly lower in women with a circumcised partner (adjusted OR = 0.18, CI 0.05–0.58). Unfortunately, there was little power to analyse within countries, due to the low prevalence of circumcision in Brazil, Colombia and Spain (five or fewer women had circumcised partners, and none of these were *C. trachomatis* seropositive). A limitation of this study was the low participation rate (serology available for only 29% of eligible women) which may limit generalizability of the study. In addition, studies of female infection and male circumcision are usually limited by lack of specific information about partners at the time of infection. In this study, however, results were similar when restricted to women who reported only one lifetime partner (OR = 0.21, CI 0.06–0.72).

**Public health issues of increased uptake of male circumcision for HIV prevention**

The data reviewed in this article raise challenges for public health. Following publication of the Orange Farm results, demand for male circumcision has reportedly increased in some countries with high HIV incidence, such as Swaziland and Zambia [42]. If the two ongoing RCT’s confirm the South African findings, countries may
HIV prevention around the implementation of male circumcision for prevention packages. There are, however, many concerns within comprehensive HIV prevention programs. In nine countries, 29–81% of uncircumcised men were willing to become circumcised, 50–79% of women favored circumcision for their partners, and 50–90% of men and women were willing to circumcise their sons. The lowest level of acceptability by uncircumcised men (29%) was from a study in eastern Uganda in 1997, before male circumcision was widely perceived as possibly being associated with STIs and HIV. Otherwise, more than half of men in the regions studied were willing to become circumcised. These studies found consistently that the main barriers to acceptability were cost, fear of pain, and safety concerns, with improved hygiene and other health benefits the main facilitators.

Conclusion

The compelling findings of the South African trials, together with the predicted dramatic impact of male circumcision on HIV rates in sub-Saharan Africa, have elevated male circumcision to the top of the list of potential new methods of HIV prevention. There is now reported increased demand for the procedure in some countries most affected by HIV, despite the fact that it is not being recommended by international agencies. If the ongoing trials show a similar impact, then safe adult male circumcision (not neonatal circumcision) is likely to be added to the current package of proven HIV prevention measures in settings with high HIV incidence. Concerns about the safety and logistics of increased uptake of male circumcision are starting to be addressed within the UN Work Plan on Male Circumcision and HIV, and will need to be expanded and continued at local country level. In addition, provision of circumcision services to young men in areas of high HIV incidence could provide a much-needed opportunity to provide education and counselling to this hard-to-reach population.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 107–108).

Male circumcision

Weiss 71


A systematic review of observational studies of male circumcision and HIV, focusing on the quality of the studies. The authors found that, after adjustment for potential confounders, most studies, including all those in high risk populations, showed a protective effect, but they were cautious in their conclusions due to variable study quality and the potential for residual confounding.


This landmark paper presents results of the first randomised controlled trial of the impact of adult male circumcision on HIV incidence. The striking results of a strong protective effect have elevated male circumcision to the top of the HIV prevention agenda.


9 Gray RH, Wawer MJ, Brookmeyer R, et al. Effect of an intervention to reduce HIV in high risk populations may provide additional benefit by protecting against other STIs.


This is the first paper to model the potential impact of male circumcision on HIV in sub-Saharan Africa. Using the estimated protective effect found in the Auvert trial, and country-level data on HIV prevalence and male circumcision, the authors estimated that 2 million new HIV infections and 0.3 million deaths could be averted over the next decade in sub-Saharan Africa.


Data from a prospective cohort study of Kenyan truck drivers were used to estimate per-sex act probabilities of female-to-male HIV-1 transmission by circumcision status. After accounting for sexual behavior, uncircumcised men were at an estimated >2-fold increased risk of acquiring HIV-1 per sex act, compared with circumcised men. The infectivity rate in this study was considerably higher than that estimated from studies of HIV-1-serodiscordant couples, which may explain the rapid spread of the HIV-1 epidemic in settings where multiple partnerships and a lack of male circumcision are common.


This is the first systematic review and meta-analysis of the associations between male circumcision and infection with herpes simplex virus type 2 (HSV-2), Treponema pallidum, or Haemophilus ducreyi. Results showed strong protective effects of circumcision on chancre size and, in some cases, a weak protective effect against HSV2 infection. These results suggest that potential male circumcision interventions to reduce HIV in high risk populations may provide additional benefit by protecting against other STIs.


This cohort study adds to the sparse literature on the effect of male circumcision on HIV transmission among men who have sex with men (MSM). Lack of circumcision was significantly associated with increased risk of HIV incidence after adjusting for confounder variables (odds ratio = 2.0).


32 A study of the distribution of HIV-1 target cells in the foreskin and glans penis, which showed that Langerhan’s cells were situated near the epithelial surface in the inner foreskin, likely due to the lack of keratinization.


38 This is one of the few studies of the role of genital hygiene in HIV infection. The study of male STD clinic attendees found a significant association between lack of penile hygiene in uncircumcised men (leading to subepithelial wetness) and HIV infection. The authors concluded that good penile hygiene should also be promoted at the community level to become a desirable social norm.


A cross-sectional study among Kenyan men recruited as sex partners of women with genital infections. In multivariate analyses, HIV infection was inversely associated with being circumcised (OR = 0.12; 95% CI, 0.02–0.91) and also independently associated with a combined measure of improved hygiene (OR = 0.41; 95% CI, 0.19–0.90).


This paper combined data from 305 adult couples enrolled as controls in one of five case–control studies of invasive cervical cancer conducted in Thailand, the Philippines, Brazil, Colombia, and Spain between 1985 and 1997. Women with circumcised partners were at a five-fold reduced risk of testing seropositive for C. trachomatis (82% reduction; odds ratio = 0.18, 95% confidence interval: 0.05, 0.58).
Sexually transmitted diseases and urinary tract infections

42 Wise J. Demand for male circumcision rises in a bid to prevent HIV. Bull World Health Organ 2006; 84:509–511.

This paper argues against introduction of male circumcision as an HIV prevention measure, for reasons including the unknown rate of surgical complications, human rights violations, and perceived 'veiled colonialism'.


Consequences of herpes simplex virus in pregnancy and their prevention
David A. Baker

Purpose of review
New findings reveal that first-time infection of the mother is the most important factor for the transmission of genital herpes from mother to fetus/newborn. Interventions based on these findings will lead to new management of the pregnant patient with genital herpes prior to pregnancy and measures to prevent the acquisition of herpes during pregnancy.

Recent findings
Risk factors for the transmission of herpes from mother to newborn have been detailed. It is the pregnant woman who acquires genital herpes as a primary infection in the latter half of pregnancy, rather than prior to pregnancy, who is at greatest risk of transmitting this virus to her newborn. This is true for both herpes simplex virus type-1 and herpes simplex virus type-2. Additional risk factors for neonatal herpes simplex virus infection include the use of a fetal-scalp electrode and maternal age of less than 21 years.

Summary
Risk factors for the transmission of herpes from mother to newborn are detailed. Antiviral suppressive therapy initiated in the late third trimester has been shown to decrease viral shedding and the need for cesarean section.

Keywords
herpes, pregnancy, prevention

Introduction
To prevent neonatal herpes simplex virus (HSV) infections, identification of the source of the infection is the primary goal of the healthcare provider. Current guidelines do not achieve this goal and new studies point to a missed at-risk population. Pregnant women susceptible to first-time genital infection with herpes are at greatest risk of having an infant born with neonatal herpes. Less than 20% of pregnant women who test seropositive for genital herpes (HSV-2) give a clinical history of having this viral sexually transmitted disease (STD). Information is accumulating on the management of the mother with established genital herpes during pregnancy. The use of divided doses of antiviral medication as suppressive therapy starting at 36 weeks gestation is receiving greater attention and acceptance.

Recent reported studies on our knowledge of the transmission of HSV to the mother and newborn, as well as the management of noninfected and infected pregnant women, are highlighted in this review. Special emphasis is placed upon the role of prevention of the transmission of this virus at the time of delivery from mother to newborn.

Epidemiology of maternal infection and maternal–fetal transmission
Genital herpes is the most prevalent sexually transmitted infection in the US and this high rate accounts for an increased risk of transmission to the newborn [1]. There is a high prevalence of genital herpes in the pregnant population. Twenty-two per cent of pregnant women test seropositive for herpes simplex virus-2. Of greater importance, 10% of pregnant women are at risk of acquisition of genital HSV from their partners, and most transmission occurs during periods of asymptomatic viral shedding from the infected partner. Two per cent of these pregnant women in the US acquire genital herpes during pregnancy [2**] and place their newborn at risk for neonatal herpes infection.

The newborn is at risk of not only the acquisition of HSV-2 but also of HSV-1. An increasing proportion of genital herpes infections are due to HSV-1, particularly among college-age populations [3]. In a study from the Midwest, HSV isolates collected from a university-student health service over a 9-year time period showed a significant increase of HSV-1 causing primary cases of genital herpes in college students. HSV-1 accounted for 78% of all genital...
isolates in their population by 2001, compared with 31% with isolates a decade earlier [3]. The increase in HSV-1 in the genital tract was greater for women in the age group 16–21 years of age. Conclusions from this study are that HSV-1 has become the most common cause of new genital herpes infections in this population in this region of the US and this reflects a reversal of the usual HSV-1/HSV-2 ratio. HSV-1 was more common in females and in younger patients, suggesting that there is a risk of HSV-1 transmission to their newborn when they become pregnant [3]. Epidemiological studies suggest that oral–genital contact is a risk factor for genital HSV-1 [3]. HSV-1 infection during childhood has declined so that more adolescents and young adults are HSV seronegative when becoming sexually active [4]. These are reasons for this increase in HSV-1 first-time infection of the genital tract in this age group.

First-time infection of genital herpes with either HSV-1 or HSV-2 in the mother in the third trimester accounts for 60–80% of neonatal herpes in the US [4]. Gardella et al. [5] studied over 3000 couples to determine the risk factors for the acquisition of herpes during pregnancy. The findings show that that HSV acquisition rates in pregnancy are high in discordant couples. Among at-risk pregnant women, HSV-1 acquisition was 2.4% and HSV-2 acquisition was 14%. Factors that were identified as risk factors for HSV-1 acquisition was partner history of oral herpes, and for HSV-2 acquisition, the duration of partnership less than 1 year. There are limitations to this study, which include large differences in the prevalence of genital herpes in different populations, and that only 47% of the male partners consented to be tested [6]. This study shows that maternal infection from the male partner during the pregnancy plays a major role in neonatal herpes infection.

Maternal genital herpes and HIV
Studies in nonpregnant women show that co-infection with HSV increases the risk of sexual transmission of HIV. Chen et al. [7] reported a study from New York City (1994–1999) examining HIV-infected pregnant women who were also diagnosed clinically with genital herpes during the pregnancy. In this study, there was a high rate of newborns infected with HIV from their mothers (11.4%). Of the total population, 5.2% (21/402) had a clinical diagnosis of genital HSV infection during the pregnancy. Of the infected women with a clinical diagnosis of genital HSV infection, 28.6% (6/21) delivered an HIV-infected infant. There was a significantly increased risk of perinatal HIV transmission from an HIV-infected pregnant woman to her newborn if she had a clinical diagnosis of genital herpes during the pregnancy. This was an independent predictor of perinatal HIV transmission.

Severe maternal herpes simplex virus disease
Genital herpes is a common disease in pregnancy. The presentation of genital herpes can be without signs or symptoms (asymptomatic primary infection) or mild recurrent disease [2]. Genital herpes can result in severe life-threatening disease, however, which needs to be diagnosed promptly and treated aggressively. A case report [8] describes a 25-year-old pregnant woman with hepatitis and acute liver dysfunction caused by HSV presenting at 34 weeks gestation. The presenting history is suggestive of genital HSV as a primary infection with dissemination to the liver. The differential diagnosis can be varied and includes other viral infections and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. With antiviral therapy, the patient recovered and delivered a viable baby. With HSV hepatitis, maternal mortality rates can be as high as 40% and can be associated with neonatal mortality rates of 40%. Severe, disseminated HSV may develop in a normal, immunocompetent pregnant woman. Fever, with flu-like illness, that progresses to hepatitis or CNS disease needs to be ruled out for HSV [9].

Diagnosis of herpes
Current recommendations or practice ask the pregnant woman and partner if they have genital herpes at the first prenatal visit [5]. This screening method fails to detect up to 90% of the women infected with genital herpes [10] and the seronegative mother as well. With new glycoprotein G-based IgG assay, clinicians can distinguish between infection from HSV-1 and HSV-2 [11]. The most recent Centers for Disease Control STD Treatment Guidelines [12] suggest that some specialists believe that type-specific serology tests are useful to identify pregnant women at risk for HSV infection and to guide counseling regarding the risk of acquiring genital herpes during pregnancy. As maternal HSV infection is so often asymptomatic [13], serology testing is reasonable. Targeted testing (looking for a high-risk population or a population with risk factors) would miss a substantial proportion of neonatal herpes. Serologic testing of the pregnant woman early in pregnancy (early second trimester) would determine which patient is infected and which is susceptible. Intervention can then be directed to management with antiviral therapy in the late part of pregnancy or to preventing infection of the mother during pregnancy. Several cost-effective models for and against this screening program have been recently published [14,15]. Women without known genital herpes should avoid sexual contact in the third trimester with partners known to have or suspected of having genital herpes. Pregnant women seronegative to HSV-1 or without known oral herpes should avoid receptive oral sex during the third trimester with partners with known or suspected orolabial herpes [12].

Management
In women already infected with genital herpes prior to pregnancy, recommendations aim at preventing HSV from coming into contact with the newborn at or around
the time of delivery. The use of antiherpetic medication as suppressive therapy starting at 36 weeks gestation until delivery has been advocated to prevent recurrent clinical HSV genital infection, reduce viral shedding and reduce the need for cesarean section [2**]. A meta-analysis of five studies using acyclovir at a dose of 400 mg three times a day starting at 36 weeks gestation in pregnant women with a history of genital herpes has been reported [16]. Acyclovir treatment late in pregnancy reduces the frequency of cesarean sections among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. In a large, well controlled prospective study, Sheffield et al. [17*] studied a total of 350 pregnant women with a history of genital herpes. Patients were divided into two groups: placebo or treated with valacyclovir 500 mg twice a day starting at 36 weeks gestation until delivery. In labor, the patients were cultures for herpes using regular culture techniques and polymerase chain reaction (PCR). In women with genital herpes, antiviral suppressive medication initiated at 36 weeks of gestational age reduced the need for cesarean delivery, and reduced viral detection from the genital tract by both culture and PCR at the time of delivery [17*]. Valacyclovir significantly reduced the number of women with clinical genital HSV at delivery by 70%, from 13% in the placebo group to 4% in the valacyclovir group (P = 0.009). Valacyclovir significantly decreased the likelihood of a positive culture or PCR result (P = 0.02). Valacyclovir decreased the number of cesarean deliveries performed for HSV, from 13% in the placebo group to 4% in the valacyclovir group (P = 0.009). At delivery, a careful inspection of the vulva, vagina and cervix should be performed. Artificial rupture of membranes should be avoided. Fetal-scalp electrodes, and vacuum or forceps delivery should be used only when critical to obstetric care, because these practices appear to increase the risk of HSV transmission.

In HIV-positive pregnant women, antiherpetic suppressive therapy should be used in those patients seropositive to HSV because of the increased risk of HIV transmission to the newborn [7]. Available data do not indicate an increased risk for major birth defects compared with the general population in women treated with acyclovir during the first trimester [18].

Prevention

In order to prevent the majority of cases of neonatal herpes, identification of the at-risk mother is the goal. Currently, recommendations do not focus on the at-risk population and nor do they identify the majority of pregnant women who are already infected with genital herpes [5*]. The first and most important step is the determination of serostatus of the pregnant woman to determine susceptibility. Routine serologic testing for the pregnant woman should be performed and is the only way to determine susceptibility of the pregnant woman by screening for antibodies to HSV-1 and HSV-2 during early pregnancy. Thus, in screening for HSV during pregnancy, both infected and susceptible pregnant women will be identified [3]. Current recommendations of the American College of Obstetricians and Gynecologists (ACOG) do not include universal testing. Prevention of neonatal HSV will depend in large part upon prevention of maternal acquisition of genital HSV in the third trimester of pregnancy [2**]. To aid in the prevention of neonatal herpes, a mandatory national surveillance system for neonatal herpes should be implemented [19].

Conclusion

A large body of information on the transmission of herpes from male to pregnant partner has been published in the recent literature. The mode of transmission from mother to newborn, mainly by maternal first-time infection in the third trimester of pregnancy, has been demonstrated. With the increasing prevalence of genital HSV infection and apparent increase in the incidence of neonatal herpes in the US, we must focus our attention on prevention of maternal–fetal transmission by the identification of the susceptible mother. Every effort to prevent transmission, by careful study and use of antiviral therapy during the last weeks of gestation, and the serological screening of all pregnant women should be considered.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 106).

Sexually transmitted diseases and urinary tract infections


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Interstitial cystitis pathogenesis and treatment
Robert Mayer

Purpose of review
Interstitial cystitis remains an idiopathic illness characterized by urinary frequency, urgency and pelvic pain with substantial morbidity in those affected. There is significant variability in the presentation, severity of symptoms and response to therapy. This review focuses on recent findings on the possible pathogenesis and potential treatments for this disease.

Recent findings
Interstitial cystitis is manifested by sensory hypersensitivity. A small volume of urine will be associated with an exaggerated sensation of pain or pressure and urinary urgency. There is continued research regarding how this process is initiated and maintained and to what extent systemic dysfunction of the immune or autonomic nervous system may play a role. The urothelial lining has been demonstrated to be capable of secreting a large number of potential signaling molecules that may be significant factors in the disease.

Summary
The pathogenesis of interstitial cystitis remains uncertain and the illness has significant diversity. Additional research is needed to establish subtypes that share common processes that can be targeted for treatment as a single effective therapy for the condition remains elusive.

Keywords
bladder, etiology, interstitial cystitis, painful bladder syndrome, review, treatment

Introduction
Interstitial cystitis is an idiopathic illness of visceral hypersensitivity characterized by increased urinary frequency/urgency and pelvic pain for which effective therapy, especially for those with longstanding/severe symptoms, remains elusive. The variability in the presentation and comorbid illnesses, whether the primary symptom is pain or urinary frequency, as well as diversity of response to therapies, suggest that interstitial cystitis be viewed as a symptom complex resulting from a variety of separate underlying but potentially interrelated mechanisms rather than a disease with a uniform pathophysiology. There continues to be controversy as to whether the problem is a specific bladder process or a manifestation of a more systemic autoimmune/endocrine disease with regional pelvic visceral/somatic dysfunction.

Diagnosis and definition
The absence of an established uniform underlying (and measurable) pathophysiology results in difficulty defining interstitial cystitis and appropriate diagnostic criteria. Interstitial cystitis was originally characterized by urinary symptoms and cystoscopic visualization of ulcerations of bladder mucosa. The number of patients diagnosed subsequently was broadened by inclusion of findings of submucosal petechial hemorrhages (glomerulations) following hydrodistension of the bladder under anesthesia. The International Continence Society [1] has proposed the term Painful Bladder Syndrome for patients experiencing a similar symptom complex. It has been reported [2], however, that a number of interstitial cystitis patients may be excluded under this new definition.

A test has been promoted for diagnosis utilizing intravesical instillation of concentrated potassium chloride and recording whether this elicits bladder discomfort [3]. Both cystoscopy and the potassium sensitivity test are reported to have shortcomings in regards to sensitivity and specificity. The literature regarding hydrodistension is complicated by the lack of a consensus in protocol/methodology in performing the procedure, with a study [4*] revealing a wide variability in the practice. It has also been recently reported [5] that the appearance of glomerulations is not constant and may develop over time.

The spectrum of severity of symptoms and the difficulties encountered with hydrodistension and potassium sensitivity testing are such that biomarkers have been evaluated as an aid to diagnosis. The most comprehensive report compared a number of putative biomarkers in...
an interstitial cystitis population. In this particular study [6], antiproliferative factor (APF) appeared to be the most specific for interstitial cystitis, suggesting its potential use in diagnostic testing. Unfortunately, the development of a reliable commercial assay for APF has yet to be developed and the control of its production and its role in actually causing symptoms remain uncertain.

Although there is a trend to make a diagnosis based on symptoms and an office test such as intravesical potassium sensitivity, interstitial cystitis still remains a diagnosis of exclusion and reasonable attempts should be made to find a correctable underlying etiology. A recent report [7**] continues to emphasize the need for thoughtful and complete evaluation of these patients as reinvestigation of patients diagnosed with interstitial cystitis resulted in only 55% having confirmed interstitial cystitis and the others having identifiable causes of voiding dysfunction.

Etiology
The etiology of interstitial cystitis is still uncertain and may consist of multiple coexisting and reinforcing mechanisms. Prevalent theories include possible infectious origin, bladder permeability defects, local neurogenic and histamine-induced inflammation, as well as a more generalized vulnerability to visceral hypersensitivity due to genetic or acquired abnormalities of the immune or neuroendocrine system.

Occult infectious origin
By definition, patients that have interstitial cystitis with symptoms should have sterile urine. The possibility that interstitial cystitis results from a chronic occult specific infectious etiology is no longer favored. Several small studies previously suggested an increased number of bacteria grown with sophisticated techniques from the urine of interstitial cystitis patients as opposed to controls. Using a prospective double-blind placebo-controlled trial with sequential oral antibiotics, however, Warren et al. [8] reported a 48% improvement in patients receiving antibiotics compared with 24% in controls, which was not statistically significant. Subsequent studies have assessed both culture data from urine and biopsies combined with molecular biology techniques for evidence of bacterial and viral products and have not found any support for a chronic infectious etiology [9*]. This does not exclude the possibility that sporadic bacterial cystitis – a historical background of many interstitial cystitis patients – may precipitate or initiate abnormal processes that subsequently lead to the condition.

Permeability defects
Abnormal bladder permeability has been proposed as a pathogenic process in interstitial cystitis, allowing toxic urinary substances to irritate the underlying tissue. The ability to clinically measure such a defect, however, has been problematic and remains elusive. Previous studies using intravesical administration of several compounds with systemic uptake measurements could not detect a difference between interstitial cystitis patients and controls. Urinary potassium levels have been measured based on the theory that the high urinary levels of potassium would provide a gradient into the bladder tissue and systemic circulation. Although there was individual variability, when analyzed by groups, there was lower potassium to creatinine ratios in patients with interstitial cystitis consistent with a permeability defect and local potassium uptake in the bladder [10*]. The most prevalent theory of altered bladder permeability is disruption of the glycosaminoglycans surface lining. In general, the weight of current evidence would support that interstitial cystitis bladders have abnormalities of protective proteoglycans but it remains unclear what molecular process causes this aberration and what role such changes may play in either initiation or continuing symptoms for individual patients. Use of urinary levels of proteoglycans as a biomarker of disease has been inconsistent. Symptom severity may be associated with levels of uronate and sulfated glycosaminoglycans [11]. Others, however, did not find a difference in total glycosaminoglycans, epitec, hyaluronic acid between controls and interstitial cystitis patients [6]. At present, although the theory of enhanced permeability and a defective bladder glycosaminoglycans layer has substantial experimental support, there is no available test for general clinical use that can accurately quantify defects in permeability or glycosaminoglycans surface abnormalities.

Neurogenic inflammation
The etiology of interstitial cystitis is still uncertain but recent advances have demonstrated that the urothelium and its innervations are much more complex than previously thought, with a variety of interrelated pathways that may in part explain interstitial cystitis pathogenesis [12**,13*]. Interstitial cystitis bladders demonstrate abnormal secretion of APF, nerve growth factor, inflammatory cytokines, ATP and multiple other signaling molecules. Abnormal production of some of these substances can persist once cells are removed from the urinary environment and grown in culture [14*,15]. These abnormalities in cellular signaling have yet to be fully explored in regards to opportunities for diagnosis or treatment. It is also unclear to what extent the diseased bladder communicates with and influences its surrounding structures. It has been shown that there appears to be increased density of nerve fibers in interstitial cystitis and that these are potentially associated with mast cells. Activated mast cells releasing histamine and other inflammatory molecules have long been suspected in the pathogenesis of interstitial cystitis but urinary histamine and histamine metabolites are not consistently found [16].
**Systemic hypersensitivity**

There is also increasing awareness in those treating interstitial cystitis that the pathology and abnormal physiology associated with interstitial cystitis may well extend outside the bladder requiring a broader view of therapeutic targets. Interstitial cystitis is a syndrome defined by bladder symptoms but it has been appreciated that interstitial cystitis patients will often have an increased prevalence of certain comorbid illnesses including allergies, irritable bowel syndrome, and fibromyalgia. When compared with the general population, the incidence of inflammatory bowel disease was estimated to be about 30 times more common than the general population in interstitial cystitis patients who had ulcers [17]. A study [18] evaluating possible genetic influences found a 17-fold greater prevalence of the disease in adult first-degree relatives of women with interstitial cystitis, suggesting a genetic predisposition to a hypersensitivity syndrome. Another study [19] has suggested a possible link between interstitial cystitis and panic disorder, with interstitial cystitis patients and first-degree relatives having an increased incidence of panic disorder as well as thyroid disease.Buffington [20] has suggested an interesting hypothesis that some interstitial cystitis patients may have a dysfunction of the balance of the neuropeptide–pituitary–adrenal axis. Evidence of such autonomic aberrations in interstitial cystitis patients includes increased resting heart rates compared with controls [21]. Interstitial cystitis patients have also been shown to have increased sensitivity to ischemia and deep pressure testing in the forearm compared with controls and this also suggests that central processing of pain is altered [22].

**Visceral neurogenic crosstalk**

In addition to the data above indicating a possible systemic dysfunction manifesting with bladder symptoms, there is increasing evidence for the interstitial cystitis symptoms being a reflection of pelvic visceral/somatic dysfunction. There is evidence for female reproductive organ irritation affecting bladder function [23]. Similar interactions with bidirectional cross sensitization can potentially occur between the lower intestinal tract and bladder [24]. It is thought that individual differences in modulation of the efferent and afferent signaling of the pelvic/bladder may involve a variety of mechanisms and in part be responsible for the lack of any single treatment to date being highly effective in this disease [25]. Studies with interstitial cystitis and control patients have verified characteristics of visceral pain syndromes with bladder hyperalgesia, although interstitial cystitis patients did not show altered sensory cutaneous thresholds in corresponding dermatomes [26].

**Treatment**

The difficulties encountered with treatment of the disease are highlighted by a review of therapies listed by patients recruited for the Interstitial Cystitis Data Base Study [27] in which 183 different types of treatment were recorded. The value of cystoscopy and hydrodistension remains a topic of debate. Some recent articles [28] have questioned the value of cystoscopy as adding little to the history and physical exam, although 56% of the patients having hydrodistension did report transient improvement.

To date, the only US Food and Drugs Association (FDA) approved therapies for interstitial cystitis remain oral pentosan polysulfate and intravesical dimethyl sulfoxide (DMSO). The mechanisms for action for both are still uncertain. Though pentosan polysulfate is designed to replace a presumed defective bladder glycosaminoglycan layer, it has also been shown in vitro to be a potent inhibitor of histamine release by mast cells [29]. The drug may also directly neutralize urinary toxic substances [30]. Only a small fraction of the oral dose reaches the bladder and appears to be the low molecular weight fraction [31]. Addition of lactose has been found to enhance bladder binding of the agent in experimental conditions but the clinical significance of this is at present uncertain [32]. The reported effectiveness of the treatment with pentosan polysulfate has been variable but most studies have noted improvement [33] and a dose escalation study did not find a benefit to increased dose but did find an apparent benefit to duration of therapy [34]. Other agents with some reported usefulness in the same class, generally administered intravesically, but occasionally as oral preparations, include hyaluronic acid [35,36] and chondroitin sulfate.

The general state of intravesical therapy for interstitial cystitis including hepanoid compounds and DMSO was recently reviewed [37]. Although diet appears to be a factor in inciting symptoms in a number of patients, the role of urinary pH is unclear, with a report [38] showing that adjustment of urinary pH did not affect symptoms.

A number of lines of evidence suggest dysfunction of the immune system in the pathogenesis of interstitial cystitis and therapies designed to correct these abnormalities have been utilized with variable effects [39]. Stimulated by a small randomized trial [40] suggesting a significant prolonged benefit of intravesical BCG, the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) sponsored a large randomized trial [41] with this agent. This trial unfortunately did not demonstrate a substantial treatment effect (21 versus 12% placebo, \(P = 0.062\)). Another approach utilized recently has been the use of cyclosporine – an immunomodulatory agent used in organ transplantation. This agent showed apparent sustained efficacy in an open label chronic study and reported superiority to pentosan polysulfate in a small randomized study, although with increased incidence of
Assessing interstitial cystitis apart from its specific bladder manifestations has led to increased interest in other adjunctive therapies as well. Many interstitial cystitis patients will have evidence of associated pelvic floor dysfunction and spasms or trigger points of these perivesical soft tissue structures are thought to potentially cause neurogenic bladder inflammation. Several reports have shown the beneficial effects of pelvic floor physical therapy on interstitial cystitis voiding complaints and pelvic pain [51]. Pelvic floor physiotherapy is likely under utilized and larger studies are needed. The ability to cope with chronic disease is variable and it has been shown that interstitial cystitis patients can be substantially troubled by depression and pain. Interstitial cystitis patients exhibiting greater catastrophizing are reported to have increased depression, pain and greater impairments of mental and social functioning. There is evidence with other chronic pain states that specific cognitive therapy and coping strategies can be helpful and have likely been underutilized in the treatment of interstitial cystitis [52**]. The effects of hormonal cycle have been documented in interstitial cystitis patients and reveal alterations of pain sensitivity and bladder functioning during the menstrual cycle. This suggests, therefore, the possibility of hormonal manipulation in patients so affected but this has not been rigorously tested [53].

Conclusion
Advances in the future treatment of interstitial cystitis will likely depend on finding methods to better identify subgroups of patients with improved likelihood of response to certain types of therapy. Given the diverse nature of interstitial cystitis, it is perhaps best currently viewed as a syndrome rather than a disease with a single uniform underlying pathogenesis that will yield to a single type of treatment for all. Multiple pathogenic mechanisms may be present and multimodal therapy, combining agents such pentosan polysulfate with antihistamines and tricyclic neuromodulators, is commonly used. Despite the frustrations of patients and clinicians, there continues to be hope that what appears to be a near uniform expression of urinary antiproliferative factor in interstitial cystitis patients will lead to advances in diagnosis and new approaches to intervention. Novel therapies in animal models or with pilot studies include gene therapy [54], Botulinum toxin [55], and new urothelial coating strategies [32*]. Earlier detection and treatment of the disease are also likely to enhance successful outcomes with currently available therapies and decrease the patient burden of this disease.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 108).

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Procalcitonin and pyelonephritis in children
Paolo Pecile and Carla Romanello

Purpose of review
In the past few years, procalcitonin has been proposed as a sensitive and specific inflammatory marker in various fields of medicine, especially in infectiology, where it has been used to discriminate between bacterial infections, viral infections and inflammation processes. Recently, different studies have emerged in the literature on the use of this marker to identify renal involvement in febrile urinary tract infections.

Recent findings
Procalcitonin seems to be a valid biological marker, with an acceptable sensitivity and specificity, which predicts a renal involvement of the infection (pyelonephritis), in comparison with the low specificity of C-reactive protein. Procalcitonin also seems to be correlated with the degree of the involvement at the moment of diagnosis of febrile urinary tract infections and with scarring.

Summary
Renal involvement has always been the main diagnostic objective in children with febrile urinary tract infections. If more studies confirm the correlation between procalcitonin, renal involvement during urinary infections and scar formation, we will finally have a noninvasive tool that can identify children at risk of complications and in need of a close follow-up as early as their first episode of febrile urinary tract infection.

Keywords
cortical scintigraphy, C-reactive protein, procalcitonin, pyelonephritis, urinary tract infection

Introduction
The diagnosis of acute pyelonephritis is traditionally based on the classical signs and symptoms such as high fever, side pain associated with pyuria, and a positive urine culture. Leukocytosis and elevations in C-reactive protein (CRP) are usually used as an ulcerior confirmation of this diagnosis [1]. An accurate diagnosis based only on these parameters often results in difficulties at the paediatric age, however, because of the aspecific nature of the signs and symptoms, especially in the infant and very small child [2].

Since the late 1980s, renal cortical scintigraphy with 99mTc-dimercaptosuccinic acid (DMSA) has emerged as the gold standard for the detection and evaluation of acute pyelonephritis and renal scarring in children. Experimental studies on pigs, using precise histopathological criteria as reference standards, have documented its great sensitivity and specificity for the diagnosis of pyelonephritis, and have also provided important information regarding renal function and the extent of renal parenchymal inflammation. Since the 1990s, the use of DMSA has clearly shown that not all febrile urinary tract infections (UTIs) are associated with a renal lesion, and that the commonly used clinical and laboratory parameters are not reliable in differentiating acute pyelonephritis from UTI without parenchymal involvement [3]. DMSA has also confirmed that scarring only occurs at sites that correspond to scintigraphic abnormalities on the initial scan, confirming the reliability of the acute-phase scan for identifying those kidneys at risk of late clinical sequelae of renal scarring, for example, hypertension, hypostenuria, proteinuria and, in the most severe and rare cases, chronic renal failure [4]. Therefore, it would seem obvious that only DMSA is able to detect children with febrile UTIs who have a risk of complications. In order to do this, do we really need to use as a ‘routine’ test an expensive examination, which is not available in every hospital and which is a source of radiation? Fortunately, most febrile UTIs are not severe infections, and following treatment with antibiotics many of the early defects seen on the pathological DMSA disappear on a control scan taken after 4–6 months [5].

As is usually the case in medicine, the choice to identify those few subjects who are expected to be at risk leads to the performance of numerous, useless screening studies at both a biological and economical cost, whereas the choice not to screen precludes the possibility of identifying subjects at risk.
The new marker

Procalcitonin, a new marker for infections, is a 116-amino acid propetide of calcitonin that lacks hormonal activity. It has been increasingly recognized as an important diagnostic tool in clinical practice. The main indications for its use and application are diagnosis of infections with systemic inflammation [6] and to monitor the therapy and the course of bacterial infections. Procalcitonin gives prognostic information and helps clinical management in sepsis as well.

Plasma concentrations of procalcitonin in healthy subjects, chronic inflammatory processes, viral infections and autoimmune disease are below 0.5 ng/ml, ranging from 0.5 to 2 ng/ml in moderate localized bacterial infections, and are above 2 ng/ml (often 10–100) in severe bacterial infections, sepsis and multiple organ failure. Its half-life is about 24–30 h in serum and it is released into the bloodstream 2–6 h after the injection of bacterial endotoxins in humans [7]. Its plasma concentration reaches a plateau in 6 h and stays high as long as an adequate stimulus persists [8]. This fast elevation due to a bacterial stimulus, in conjunction with a rapid downfall of its concentrations by 48 h after the administration of an effective antibiotic therapy, make procalcitonin a precocious and sensitive marker for severe bacterial infection, to be used not only for diagnostic revelations but also for patient monitoring and response to therapy.

Correlation between procalcitonin and pyelonephritis

In 1998, Benador et al. [9] measured procalcitonin levels in an attempt to differentiate acute pyelonephritis from lower tract infections. The goal of their study was to verify if procalcitonin was able to predict renal involvement as assessed by DMSA in their patient population of 80 children with febrile UTI. Before beginning therapy, determination of WBC, CRP and procalcitonin was made. Within 5 days of admission, all children underwent DMSA scintigraphy and the lesions were graded into five categories (absence of lesions, very mild, mild, moderate and severe). When procalcitonin and CRP were correlated with the severity of the renal lesions, they found a poor correlation with plasma levels of CRP. For the prediction of early renal lesions, CRP at the cut-off suggested in the literature (20 mg/l) [1] had a sensitivity of 100% and a specificity of 26%. In other words, its low specificity limited its clinical usefulness since it leads to considerable confusion about pyelonephritis of UTIs without renal lesions. In contrast, a high significant correlation with procalcitonin plasma levels was found. At the cut-off of 0.5 ng/ml, procalcitonin specificity was found to be much higher (82.6%). The most interesting data, however, were that all patients with moderate and severe scintigraphic lesions had procalcitonin values higher than 0.6 ng/ml, and children who showed lesions with DMSA even though they had normal procalcitonin values (sensitivity 70.3%), had very mild or mild lesions. Furthermore, procalcitonin values correlated with the follow-up scan showed a trend towards a positive correlation with partially reversible lesions (scar). The significant correlation between procalcitonin and renal involvement was reported in two other studies [10,11].

A few years after Benador’s study, our group [12] studied procalcitonin in the same manner with the goal of determining the accuracy of procalcitonin levels compared with CRP levels, in diagnosing renal involvement during febrile UTI and in predicting subsequent scars. One hundred children were enrolled at their first febrile UTI occurrence. WBC, CRP and procalcitonin were measured before starting antibiotic therapy. Renal parenchymal involvement was verified with a DMSA scan within 5 days of admission. A five-group score (0–4) was assigned for renal involvement. For the prediction of pyelonephritis, CRP levels at the cut-off level of 20 mg/l had a sensitivity of 94.4% and a specificity of 31.9%. In contrast, procalcitonin levels, at the cut-off level of 0.8 ng/ml, had a sensitivity and specificity, respectively, of 83.3% and 94.4%. When levels of CRP and procalcitonin were correlated with the extent of renal involvement, as assessed by DMSA, a highly positive correlation was found only with procalcitonin plasma levels, and mean procalcitonin values for the five groups of patients were positively correlated with increasing scintigraphic score. In our study, mean procalcitonin levels in children with scarring at follow-up DMSA were higher than in children with reversible lesions, findings that were similar to previous studies.

Correlation between procalcitonin and scarring

Subsequently, Prat et al. [13] evaluated the usefulness of procalcitonin measurements to distinguish between uncomplicated UTIs and pyelonephritis with renal scarring, comparing the results with other inflammatory markers. A DMSA scan was performed 5–6 months after UTI in 77 children (1 month to 12 years). Serum samples for procalcitonin were taken at admission and, when possible, 24 h later. Scars were detected in 13/77 children (16%). In clinically proven lower UTI, procalcitonin values were very low and remained so on the second determination; in contrast, in pyelonephritis with scars, procalcitonin was elevated and still high 24 h later. Interestingly, some of the patients (14) with clinical diagnosis of pyelonephritis showed low values at admission but increased values on the second determination. None of these patients developed scars. Low CRP specificity was confirmed (34.4%) in detecting scarring, unlike procalcitonin, which showed a sensitivity of 92.3% and a specificity of 61.9%. The authors concluded that procalcitonin
had a high negative predictive value of renal damage, and a low procalcitonin level at the time of diagnosis of UTI was prognostic of a low risk of renal scarring.

**Recent findings**

In spite of these interesting results, only three studies have been published in the past year concerning the correlation between procalcitonin and pyelonephritis at paediatric age. Of these studies, two confirmed that procalcitonin is a reliable marker for detecting renal lesions during febrile UTIs. In both of these studies, procalcitonin and CRP were determined before beginning antibiotic therapy, and renal involvement of the infection was assessed by DMSA. In one of the studies [14], in which 76 patients were enrolled, DMSA scans were performed within 7 days. Using a cut-off of 0.5 ng/ml for procalcitonin and 20 mg/l for CRP, sensitivity and specificity in detecting renal lesions in febrile UTI were, respectively, 58% and 76% for procalcitonin, and 94% and 58% for CRP. In the other study [15] (42 patients enrolled), DMSA scans were performed within 72 h. For procalcitonin serum levels of at least 0.5 ng/ml, sensitivity and specificity in detecting renal lesions were, respectively, 100% and 87%, while for CRP levels of at least 20 mg/l, a 94% sensitivity and a 30% specificity were found. In contrast with these results, the third study, a recent short report [16], has shown that procalcitonin’s sensitivity and specificity for detecting renal lesions during febrile UTIs were, respectively, 68% and 23%, using a cut-off of 0.5 ng/ml.

As shown in Table 1, most studies, where procalcitonin was correlated with renal lesions during febrile UTIs, proved that procalcitonin had a discrete sensitivity, as well as specificity, to predict renal lesions even though its diagnostic accuracy is very variable, especially in the most recent studies. This is probably due to the small and heterogeneous population of patients chosen and to different interpretations of DMSA scans. In fact, it is known that interpretations of scan images are often influenced by the operator’s subjectivity, especially in doubtful or small-entity lesions, and that sometimes it is not easy to differentiate between acute lesions and past outcomes of febrile UTIs. For this particular reason, differentiating DMSA scans simply as ‘pathological’ and ‘nonpathological’ can be a very rough estimate and may result in an important confounding factor. In order to judge the accuracy and predictive capacity of this new marker, it is necessary to demonstrate a correlation between procalcitonin levels and the grading of the lesion. Since DMSA scans during febrile UTIs may show different grading of renal lesions, and since in both Benador’s and our studies, sensitivity and specificity improved with the increase of renal involvement on DMSA scans, the diagnostic accuracy of procalcitonin is dependent on the grading of renal lesions as assessed by DMSA.

**Conclusion**

The paediatrician faced with a child with febrile UTI has always needed to differentiate a low UTI from pyelonephritis, and has been forced to consider the necessity of executing invasive assessments and the fear of them being useless. The conclusion drawn from clinical experiences is that procalcitonin, compared with CRP, has demonstrated a better ability to discriminate febrile UTIs with renal involvement from those without it, because of the unquestionably low specificity of the latter. This is an essential aspect, not only for treatment, but especially for the follow-up and long-term prognosis.

Concerning the first difference, procalcitonin is selectively induced during systemic inflammation of bacterial origin and differentiates from viral diseases [17]. In contrast, CRP is an extremely sensitive marker that is induced not only by bacterial diseases but also by many viral infections, so that, at the moment, data do not support a role for CRP in the differential diagnosis between viral and bacterial infections [18]. Furthermore, in UTIs, its main limitation remains its low specificity as a predictive marker of acute renal lesions during UTIs [3].

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of patients</th>
<th>Cut-off (ng/ml)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV%</th>
<th>NPV%</th>
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<tbody>
<tr>
<td>Benador [9]</td>
<td>1998</td>
<td>80</td>
<td>0.5</td>
<td>70.3</td>
<td>82.6</td>
<td>85.7</td>
<td>97.6</td>
</tr>
<tr>
<td>Smolkin [11]</td>
<td>2002</td>
<td>64</td>
<td>0.5</td>
<td>94.1</td>
<td>89.7</td>
<td></td>
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<tr>
<td>Pecile [12]</td>
<td>2004</td>
<td>100</td>
<td>0.8</td>
<td>83.3</td>
<td>93.6</td>
<td>93.7</td>
<td>83.0</td>
</tr>
<tr>
<td>Bigot [15] *</td>
<td>2005</td>
<td>42</td>
<td>0.5</td>
<td>100</td>
<td>87</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>Gurgoze [14] *</td>
<td>2005</td>
<td>76</td>
<td>0.5</td>
<td>58</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuerlinckx [16] *</td>
<td>2005</td>
<td>63</td>
<td>0.5</td>
<td>68</td>
<td>23</td>
<td></td>
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NPV, negative predictive value; PPV, positive predictive value.

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The second difference is characterized by their kinetics: procalcitonin is induced very rapidly by an infective stimulus and within 6–12 h reaches its plateau, which lasts as long as the stimulus persists, while CRP is induced more slowly than procalcitonin (<12 h), reaches a peak after 36–50 h and its production in the liver continues for several days after the inflammatory stimulus has abated [18]. This difference is not to be underestimated since frequently a febrile child is immediately brought by his parents to a doctor’s attention, and a low CRP associated with a positive urine culture might mislead the physician to think of a lower UTI.

Both from the literature and from personal experience, for all of those who have dealt with UTIs in paediatrics, it is evident that knowledge in this field has changed significantly: thanks to DMSA, we understand that in many febrile UTIs, a renal involvement is not demonstrated, that the majority with pyelonephritis recover without sequelae, that vesico-ureteral reflux is not always present in children with pyelonephritis, and that many kidneys with reflux do not necessarily lead to pyelonephritis. Furthermore, through a more accurate and critical revision of studies from past literature, we have become conscious that the worst long-term complications rarely happen as a consequence of pyelonephritis in kidneys that were initially found to be normal. The evident consequence of this knowledge is that probably the majority of children with febrile UTIs do not need invasive assessments and that new diagnostic strategies need to be found to select those few children that indeed have a risk of long-term complications, avoiding if possible invasive assessments such as DMSA and cystography.

The search for a reliable marker of renal lesion during UTIs follows this strategy, as it should. On this matter, a recent French study should be mentioned that demonstrated a correlation between procalcitonin levels and the presence and grade of reflux [19]. The same results have been confirmed in a European multicentric study that gathered an extensive population and documented how procalcitonin represented a strong, independent and now validated predictor for vesico-ureteral reflux [20].

How procalcitonin may embody the first step of this new strategy and, particularly, how reliable it may be in replacing DMSA, which is still considered the gold standard for the diagnosis of pyelonephritis, are yet to be determined.

Although the number of studies published are limited, procalcitonin has, however, demonstrated some specific characteristics that make it more reliable than CRP in highlighting renal lesions during UTIs. These are, firstly, the velocity with which it is induced by the infectious stimulus, which increases somehow its high negative predictive value; second, the better specificity compared with CRP in detecting renal involvement during febrile UTIs; and lastly, but maybe the most interestingly, even though documented in only two studies, the progressive increase of its blood concentration with the increase of the renal lesion’s entity.

In conclusion, for the time being, procalcitonin can be considered an accurate and sufficiently reliable new biological marker to be used in clinical treatment of febrile UTIs.

Further large and possibly multicentric studies using rigorous methods are necessary to confirm the effectiveness of procalcitonin in detecting renal parenchymal lesions during UTIs and, especially, their extension. If what seems to have emerged is confirmed, the first step of a new diagnostic strategy for children with febrile UTIs might be to use procalcitonin as a screening examination to precociously identify children with renal lesions who need ulcer assessments and a closer follow-up.

Acknowledgements
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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
** of special interest
• of outstanding interest

Additional references related to this topic can also be found in the Current Literature section in this issue (p. 106).

Procalcitonin and pyelonephritis in children


Prospective study. In spite of low sensitivity procalcitonin keeps discrete specificity for the diagnosis of acute pyelonephritis.

Prospective study. Little case study. Excellent procalcitonin sensitivity and low CRP specificity were confirmed.

Prospective study. The only work which, at the cut-off of 0.5 ng/ml, does not confirm reliability of procalcitonin in detecting renal lesions in UTIs but the raise of cut-off confirms discrete specificity.


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The management of HIV and hepatitis B co-infection

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The management of HIV and hepatitis B co-infection

The number in square brackets following a selected paper, e.g. [7], refers to its number in the annotated references of the corresponding review.

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This bibliography is compiled by clinicians from the journals listed at the end of this publication. It is based on literature entered into our database between 1 October 2005 and 30 September 2006 (articles are generally added to the database about two and a half months after publication). In addition, the bibliography contains every paper annotated by reviewers; these references were obtained from a variety of bibliographic databases and published between the beginning of the review period and the time of going to press. The bibliography has been grouped into topics that relate to the reviews in this issue.

- Papers considered by the reviewers to be of special interest
- Papers considered by the reviewers to be of outstanding interest

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Highly active antiretroviral therapy in HIV management


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