Science, sense, and nonsense about HIV in Africa

Angus Nicoll, Japhet Killewo

The 13th international AIDS conference is being held in Durban, South Africa in July 2000. The setting is highly appropriate as nearly 70% of all HIV transmission and people living with HIV infection are in sub-Saharan Africa. Between a third and a quarter of young adults are infected with HIV in some parts of southern Africa[1]. In east and central Africa, where the virus has been present longest, HIV is reducing adult life expectancy and reversing the advances made in child survival and tuberculosis control in the past 25 years[2-4]. It burdens an already strained health and economics systems and is prejudicing the future development of Africa as a whole[5].

Successful HIV prevention depends on political commitment. The two countries in Africa that have been most successful in reducing or containing HIV transmission are Uganda and Senegal, where from the start there has been strong national leadership in AIDS prevention[6-9]. It is therefore alarming to read press accounts of doubts at the highest leadership level in South Africa about whether HIV infection causes disease and death[10,11].

Questions about the links between HIV, AIDS, and mortality have been expressed since the early 1990s[12], when a few scientists (notably none with significant public health or microbiology experience) raised the issue, the most prominent being Professor Peter Duesberg[13]. Their doubts were promulgated by self-styled 'AIDS dissidents' and, like many apparent controversies between scientists, the topic generated good copy for some journalists[14]. The scientific evidence that HIV infection is pathogenic and the prime cause of AIDS was strong then and is even stronger now. Perhaps the single most definitive African evidence comes from Uganda, where the joint Ugandan-UK (Medical Research Council) programme has worked for over ten years with the population-based Masaka natural history cohort. That study found that five year death rates in adults with HIV infection were 11 times as high as those in uninfected adults. HIV was present in 8% of the population but that proportion accounted for 40% of all adult deaths[15].

> '...70% of all HIV transmission and people living with HIV infection are in sub-Saharan Africa...'

Other cohort studies in Africa have also reported increased premature mortality in people with HIV infection[16]. Independent supporting evidence comes from several sources. The 1990 census of Uganda found significant erosion of young adult and early childhood populations where HIV was most prevalent[17]. Data from demographic health surveys indicated substantial rises in mortality in men aged 16 to 60 years between 1986 and 1997 in Malawi, Tanzania, Uganda, Zambia, and Zimbabwe that can be explained only by the advent of HIV[18]. The relationship between HIV infection and AIDS is also supported by a dramatic reduction in AIDS incidence and mortality since 1996 among people with HIV infection in countries wealthy enough to make widespread use of highly active antiretroviral therapy (HAART)[20]. Those who would deny HIV is a pathogen must explain this evidence from Africa and developed countries.

For the uninformed newcomer to the field several sources of confusion exist – for example, there are reports of long term survivors with HIV, people who develop AIDS without HIV infection, and people with HIV who die without developing AIDS.

Almost all infections vary in their effect on individuals but long term disease free survival with HIV is rare (under 5%) without antiretroviral treatment[21]. In the Masaka cohort after five years 54% of those initially found to be infected had died and even in well resourced northern countries (before HAART) nearly 50% of young men who acquired HIV infection had died within 12 years[15,19].

It is sometimes forgotten that 'AIDS' is an artificially constructed case definition, devised for surveillance purposes when the cause of the new disease was unknown[22]. Because it has to apply universally, even where HIV testing is not available, and because some individuals decline to accept HIV testing, the AIDS case definition has always been constructed to function without the requirement of an HIV test result[23]. There have always been rare conditions in which individuals can meet the AIDS case definition without being HIV infected[24]. When national surveillance systems have examined reports exhaustively for such people, however, and excluded those for whom an HIV test result is not available, the numbers of cases with repeatedly negative HIV test results are vanishingly small[25].

The AIDS case definition was also constructed to be as specific as possible, usually utilising unusual

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opportunistic infections that occur rarely in immunocompetent individuals. HIV leaves the human body equally vulnerable to conventional bacterial pathogens, hence people can die as a result of HIV infection without meeting the AIDS case definition[26]. This is especially so in African settings where treatment for conventional bacterial infections may not be available and where even the AIDS-defining infection of *M. tuberculosis* may be missed[27].

Concerns, confusion, and myths about HIV will persist. Doubt and seeming disagreement between scientists is newsworthy and may be exploited by people with axes to grind. It is also natural for people to grasp seeming good news and 'AIDS myths'[28], no matter how incredible, particularly when facing such an overwhelming problem as HIV[29]. Sometimes it is suggested that ignoring doubts and myths denies them credence. In our experience, however, when doubts and myths are left unchallenged, the result is denial and a lack of action in political, public health, and individual terms needed to fight HIV.

Scientists who wish to challenge the HIV hypothesis that HIV infection is a significant human pathogen should publish evidence for their contentions in reputable journals for evaluation by the scientific community rather than engaging politicians and news media to threaten rational programmes that are proven to educe HIV transmission. Some may argue that the self-styled dissidents have been excluded from scientific debate[11]. This is not so, but the scientific community cannot lower its standards of evidence for special interest groups[30].

President Mbeki has called for African solutions to HIV in Africa[11]. This is right and proper. Heterosexual transmission is more important in Africa than in rich industrialised countries, and HAART will rarely be affordable in resource poor settings[31]. Nevertheless there are already good African models of how to reduce HIV transmission and how to care for those with HIV in Africa[6-9,31]. Now there is also a new International Partnership Against AIDS in Africa to fund such solutions[5]. That is the correct path to pursue, rather than denying the pathogenicity of HIV and suggesting that scientists from Africa and elsewhere have got AIDS and HIV all wrong for the past decade and a half.

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Medical mycology in the UK: time to stop the dry rot

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The specialty of medical mycology has been in decline for some years in the United Kingdom (UK) and it is now approaching a manpower crisis. It is ironic that the fungi, which have their own kingdom in the classification of life forms, should find themselves with precious little royalty and almost no courtiers. How has this come about and does it matter?

Many outside the specialty regard fungal infections as relatively trivial and that fungi are largely innocuous organisms. As a result service laboratory work is given a low priority and is often carried out by technical staff with limited training in mycology. A survey performed by a joint working party of the British Society for Antimicrobial Chemotherapy and this society in 1996 found that '...the response of diagnostic laboratories (to fungal infections) was sometimes suboptimal...' and that a 'great reliance on the reference laboratories was revealed...'[1].

Despite this continued under-appreciation of the specialty, the demands on medical mycology are increasing. In 1999, 2682 solid organ transplants were performed in the UK[2], and about 20% of the recipients are likely to have suffered invasive fungal infections[3]. In 1998, 1963 stem cell transplants were carried out in the UK, in line with a fourfold increase in Europe since 1991[4]. There are no good data on the total number of leukaemic patients treated with chemotherapy alone, but the number of neutropenic episodes resulting from this that were managed in the past year is likely to be at least 8000. The prevalence of HIV infection continues to rise and by the end of last year, out of a total of 40372 recorded cases of HIV infection, 5044 patients surviving with a diagnosis of AIDS were being managed in the UK[5].

'medical mycology... ...is now approaching a manpower crisis'

These data give some idea of the numbers of patients most at risk of invasive fungal infections, but take no account of those receiving high dose corticosteroids or parenteral nutrition, patients with solid tumours or diabetes, neonates in hospital, and surgical patients (still the largest group of patients with candidaemia)[6], among others. Dermatophyte infections may affect between 8% and 40% of the general population and the prevalence of nail infections is estimated to exceed 2%[7]. *Trichophyton tonsurans* infection, which often causes severe scalp scarring, has been spreading, often unrecognised, among children in recent years. This emphasises the need for expert diagnostic skills in the laboratories that serve dermatology clinics.

An estimated 600 cases of candidaemia were treated in the UK in 1996[1], but this is likely to have been a considerable underestimate; in the United States *Candida* species are now the fourth commonest blood culture isolate[8]. Aspergillosis has increased 14-fold in little over a decade in Europe[9], reflecting the expanding at-risk population. These, along with cryptococcosis, are the commonest invasive fungal infections affecting the immunocompromised population. In addition, however, more and more unusual fungi, requiring considerable taxonomic expertise, are being found in patients with impaired immunity.

Hospitals in the UK spent £30 349 300 on systemic antifungals in 1999 (an increase of 18% over 1998; data source: Medicare Audits Ltd. Hospital Pharmacy Audit Index, December 1999) and overall expenditure in general practice was £37 197 300 (an increase of 8%; data source: IMS Healthcare Ltd, British Pharmaceutical Index, December 1999). Despite these enormous sums spent on prescribing, the number of senior mycologists in the UK has fallen steadily in recent years. Fewer than 10 senior scientists now serve the whole population, and three are likely to retire in the next eight years.

How can we reverse this decline? The source of potential senior scientists lies in the academic departments and the developing pool of clinical scientists. We need to encourage able mycologists to remain within the specialty. Modern medical mycology stands at the interface between several areas of biology of fundamental and increasing significance – molecular biology, cell biology, and immunology. We have recently begun to understand the plasticity of both genotype and phenotype displayed by these organisms. Fungal infections can be used to model disease processes – such as lung fibrosis and disease reactivation. The ability of fungal infections to spread rapidly may also yield information about the specificity or otherwise of interactions at the host-pathogen interface.

The diversity of fungal infections (superficial / disseminated, opportunist / primary pathogen,

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cosmetic/life-threatening) offers tremendous scope for scientific investigation at all levels. It is at the level of doctoral research, however, that the opportunities described above will be successfully exploited. In order to attract young scientists and clinicians into the field mycology needs a higher profile at the undergraduate and MSc levels; young researchers cannot be blamed for ignoring a field whose existence is barely acknowledged. A small and relatively subtle increase in exposure to mycology backed by enthusiastic promotion by relevant educational bodies would make a substantial difference. Funding such an increase requires public support, which will require the cooperation of several professional bodies, the media, and government organisations. Between five and 10 university and NHS departments already run PhD/MD programmes of research into fungal diseases. We need to link this with the service and reference components of the specialty.

We need to establish new posts in departments where interest and expertise already exist to provide a suitable training and career structure for the specialty. These are needed in order to supply clinical scientists able to replace those approaching retirement and to provide a modern and dependable mycology service. The UK's antifungal budget, approaching £70 million, justifies an infrastructure consisting of reference laboratories of international status and a network of regional laboratories able to support and guide the management of superficial and invasive fungal infections. Mycologists look to the support of our clinical and laboratory colleagues in our efforts to achieve this.

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Is the polymerase chain reaction a useful tool or an expensive toy in culture-negative endocarditis?

John Moore, Cherie Millar

Infective endocarditis is a non-contagious infection of the valves of the heart. Heart valves damaged by congenital heart disease or rheumatic fever are more susceptible to infection. The risk of infection is further increased by major dental treatment, genitourinary instrumentation, the presence of artificial heart valves, excess alcohol consumption, immunosuppressant drugs, or injecting drug use[1]. Infective endocarditis may be fatal if not diagnosed accurately and promptly and may lead to complications such as thrombosis, stroke, cardiac arrhythmias, abscesses, and other septic complications including meningitis and pneumonia. Endocarditis is often curable if diagnosed early and treated with appropriate antibiotics, usually for four to six weeks[2]. If the diagnosis is delayed or missed, however, or if a fungal infection is responsible, valve replacement may be needed.

Swift and accurate clinical and laboratory diagnosis of infective endocarditis is vital and is helped by the use of the 'Duke' criteria (summarised in the table)[3]. The major criteria are an abnormal transoesphageal echocardiogram and/or positive blood culture results, and there are several minor

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TABLE Major and minor criteria for the classification of endocarditis according to the Duke Endocarditis Service[3]

Major criteria	Minor criteria	Diagnosis
1. Positive blood culture • typical organism in >2 blood cultures in the absence of a primary focus [*Staph aureus*, enterococci, viridans streptoccocci, *Strep bovis*, HACEK*] • persistently positive blood culture **2. Evidence of endocardial involvement** • positive echocardiogram (TOE) • new valvular regurgitation	**1. Predisposition** • heart condition • drug abuse **2. Fever** • >38°C 3. **Vascular phenomena** • major arterial emboli • Janeway lesions • septic pulmonary infarcts **4. Immunological phenomena** • Osler's nodes • Roth spots • rheumatoid factor • glomerulonephritis **5. Microbiological evidence** • positive blood culture not meeting major criteria • positive serology **6. Endocardiographical evidence** • consistent with infective endocarditis but not meeting the major criteria	**1. Definite** • 2 major • 1 major and 3 minor • 5 minor • pathology/histology findings **2. Possible** • findings fall short of the definite categories but not rejected **3. Rejected** • alternate diagnosis • resolution of the infection with antibiotic therapy for 4 days or less • no pathological evidence after antibiotic therapy for 4 days or less

* HACEK: *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*

criteria. No organism is cultured from blood in between 5% and 24% of cases, due to prior antimicrobial chemotherapy, fastidious organisms, cell-dependent organisms such as *Coxiella burnetii* and fungi, and non-infective endocarditis associated with immunological phenomena and non-bacterial thrombotic endocarditis.

The overall incidence of culture-negative endocarditis varies from country to country, being higher in undeveloped and developing nations (for example, 60% in Ethiopia), and lower in developed nations (for example, 1.1% in the Netherlands)[2]. Access to better diagnostic technology in clinical and laboratory settings, including transoesophageal echocardiography and improved culture techniques, probably explains why fewer cases of infective endocarditis are missed in the developed world. The adoption of prolonged incubation times (10-21 days), the presence of carbon dioxide, enriched culture media, supplementation with various growth factors (L-cysteine or pyridoxal) and timed sub-cultures, and the practice of withdrawing antibiotic chemotherapy for a short period to allow blood cultures to become positive in routine bacterial culture means that organisms that were often missed using less sophisticated techniques are now being recognised. The newer methods have enabled the identification of *Streptococcus adjacens* and *S. defectivus*, which had previously been designated nutritionally variant streptococci and 'difficult to culture'. The HACEK group of organisms (see table footnote) and *Brucella abortus*, *B. melitensis* and *Mycobacterium* spp are now easier to detect using modern continuously-monitoring blood culture systems, such as the BactAlert or Bactec systems[4]. The identification of pathogens responsible for cases of infective endocarditis previously dubbed 'culture-negative' is fundamental to the selection of appropriate antimicrobial chemotherapy.

> 'this resource ...requires rigorous controls, validation, and optimisation'

Molecular biology has made much progress in identifying new agents associated with well-known and newly emerging infectious diseases. Fastidious organisms such as *Bartonella* (*Rochalimaea*) *quintana* have been identified in patients suspected to have bacterial endocarditis. Various groups have examined the employment of nucleic acid amplification techniques to detect the pathogens responsible for culture-negative endocarditis[5,6]. Our research group at the Northern Ireland Public Health Laboratory has just taken part in a three year study on the molecular diagnosis of infection using universal rRNA polymerase chain reaction (PCR), which may offer an alternative to the traditional methods used to identify pathogenic and commensal bacteria – isolation or propagation in the laboratory. Biochemical, morphological, and serological tests usually require growth of the organism. Reliance on these parameters is often impractical and has limited our awareness of the diversity of bacterial pathogens responsible for infective endocarditis. 16S rRNA genes, found in all bacteria, are being used increasingly for phylogenetic, evolutionary, and diagnostic studies. 16S rRNA sequences accumulate mutations at a slow, constant rate, and may therefore be used as 'molecular clocks'[7]. Highly variable portions of the 16S rRNA sequence provide unique signatures to any bacterium and useful information about

relationships between them. Alternatively, since 16S rRNA molecules have crucial structural constraints, certain conserved regions of sequence are found in all known bacteria. 'Broad-range' or 'universal' PCR primers may therefore be designed to recognise these conserved bacterial 16S rRNA gene sequences and used to amplify intervening, variable, or diagnostic regions. Most importantly, this PCR procedure avoids the need to grow the bacterium and requires no pre-existing phylogenetic information.

In our experience the application of PCR accompanied by direct automated sequencing of the PCR amplicons helps to detect causal organisms directly from blood culture material, when continuously-monitoring blood culture systems such as the BactAlert system have been consistently negative. Under optimal conditions, molecular detection and identification of any non-culturable pathogen in culture-negative infective endocarditis takes about 48 hours. We have detected several clinically significant organisms, such as *Bartonella* spp. and *Candida albicans*, which would have been missed by routine blood culture. Use of the molecular assay has enabled us to select appropriate antimicrobial chemotherapy.

The technique yields high quality data, which are clinically very valuable if the blood culture sets have been submitted from appropriate patients – who fulfil the Duke criteria for infective endocarditis. If not, the expensive laboratory work yields results of little clinical value. Laboratory-induced false positive results may arise due to contamination. Close communication between the cardiologist and the medical microbiologist is needed to ensure that appropriate patients are selected for molecular analyses. Careful controls and a battery of laboratory precautions, such as isolated bench space for universal PCR set-up reduce the problem of contamination. We would encourage the adoption of such techniques in specialist molecular laboratories that perform PCR and have a practical appreciation of the problems associated with universal PCR, as quality results depend on full awareness of the clinical background through consultation with cardiologists and its implications.

In well defined cases of culture-negative endocarditis, nucleic acid amplification using one of the many molecular platforms currently available (including NASBA, TaqMan, LightCycler, and conventional liquid PCR) should be performed. Both 16S (bacterial) rRNA and 18S / 28S rRNA (fungal) amplification should be followed by automated sequence identification of the amplicons. PCR and automated sequencing may be useful tools for the detection of the agents that cause 'culture-negative' endocarditis, but this resource must be managed properly, as it is not an easy assay to perform consistently and requires rigorous controls, validation, and optimisation. Perhaps the service should be confined to a small number of regional diagnostic laboratories, experienced in universal rRNA PCR, who are willing to provide a quality service for a small number of well-defined cases. Otherwise, we do chance having ubiquitous, expensive, and redundant toys.

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Preventing transmission of bloodborne virus infections in prisons

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This issue of *Communicable Disease and Public Health* includes a report of one of the largest ever surveys of bloodborne virus infection among prison inmates[1]. Andrew Weild and colleagues provide evidence of the extent of drug injecting and sharing of injecting equipment in English prisons and of the prevalence of hepatitis C virus (HCV) among inmates who have ever injected drugs[1]. The analysis of behavioural data suggests but cannot prove, due to the study design, that HCV infections were acquired inside prison. It is hard to prove that HCV transmission occurs in this setting because acute infection rarely causes symptoms[2] and because cohort studies (needed to estimate incidence) are hampered by such logistical problems as the brevity and interrupted nature of most prisoners' sentences. A study of the incidence of HCV infection among men incarcerated in a Scottish long-stay prison is under way.

HCV transmission inside prison has been confirmed in Australia (four cases)[3], and data from cross sectional surveys of injectors have shown that admission to, and injecting within, prison are independent determinants of HCV infection[4,5]. It is important that investigators continue to accumulate data on the acquisition of HCV inside prison, but those who use the current paucity of direct evidence to deny that HCV is transmitted in this setting are guilty of neglecting the public health. Injecting in prison is associated with the random sharing of injecting equipment[6] and HCV is spread through such activity[7], so it is absurd to deny that this infection is likely to be a major problem in UK prisons. This is not to say that prison is the main setting in which HCV is spread. Injectors are much more likely to become infected outside prison because far more injecting and needle and syringe sharing occurs outside than inside: over 30% of non-incarcerated injectors in the UK inject frequently with used equipment and the proportion is increasing[8,9].

> 'Keeping injectors out of jail should be a priority'

The prevention of HCV among injectors in all settings is a much greater challenge than that for HIV because the prevalence of HCV is higher[1,8,10] and its infectivity is greater[11]. HIV transmission among injectors in the UK has become an infrequent event anywhere[1,8,12]. Needle and syringe exchange[13-15] and methadone maintenance programmes[16-18] in community settings have reduced the chaotic sharing of injecting equipment by, and thus the spread of HIV among, injecting populations. Furthermore, over 90% of HIV infected injectors in the UK know their HIV status[8] and many are taking antiretroviral drugs that lower viral load. There is a low probability that an HIV infected injector who enters a network of injectors who share injecting equipment in prison will be infectious. Accordingly, community-based interventions to reduce the sharing of injecting equipment have been sufficient to stave off HIV transmission in UK jails despite the rudimentary nature of the prevention initiatives implemented in prisons. The outbreak of HIV among injector-inmates in HMP Glenochil in 1993[6] showed, however, that – given the right conditions – HIV can spread rapidly in prison.

The incidence of hepatitis B virus (HBV) infection among injectors rose steeply in the late 1990s[8] and a simultaneous increase in cases in Scottish prisons led to HBV vaccination being offered to inmates throughout Scotland (Alan Mitchell, personal communication). This initiative, while laudable, does nothing to solve the problem of sharing injecting equipment or to reduce the risk of HCV infection. An estimated 39%[1] of injector inmates in England and 56%[19] in Scotland are HCV antibody positive. In Glasgow the current annual incidence of HCV infection among injectors is between 20% and 30%; more effective interventions are needed to reduce the sharing of injecting equipment inside and outside prison.

Keeping injectors out of jail should be a priority. Methadone maintenance therapy is not a panacea but it does reduce a drug user's need to acquire drugs illegally and thus commit crime[16,18]. The UK's community-based methadone services have improved but they are still patchy and often stretched to capacity; further expansion would lead to less imprisonment of injectors. Experience in the United States of replacing prison sentences for minor drug-related offences with compulsory drug treatment stints suggests that this approach deserves to be developed and evaluated[20]. It would be naïve to expect prison authorities to support calls to provide injector-inmates with sterile needles and syringes. The prison officer's job

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is difficult enough without having to grapple with the practical and ideological implications of a policy that would overtly condone illicit drug taking and injecting.

The Home Affairs Select Committee concluded in its November 1999 report *Drugs and Prisons*[21] that 'disinfection materials should be provided (in prison) but not needle exchanges'. Bleach tablets were made available to inmates in UK prisons in the mid 1990s[22] but were withdrawn from English and Welsh establishments because of concerns about health and safety and have yet to be reintroduced. The results of a pilot study to assess the feasibility of distributing tablets safely among inmates have been encouraging (Andrew Weild, personal communication) but the extent to which the provision of bleach in this setting prevents bloodborne infections remains uncertain[23,24]. The provision of bleach to inmates might be construed as a harm reduction method, which condones drug taking. Bleach is accessed by inmates for various purposes, however, and its use to clean needles and syringes is a clandestine activity that requires no declaration of intent to prison staff. Accordingly, prison authorities regard this approach as more acceptable than the distribution of needles and syringes to prisoners.

Assuming that the provision of needles and syringes in prison remains taboo, other harm reduction approaches must be developed. Inmates who do not wish to engage in drug-related activity should be given the opportunity to be held in drug-free environments[25]. For prisoners who are committed to taking drugs (particularly opiates) the only accepted way to ensure that this practice is safe and legitimate is to prescribe them maintenance therapy in the form of methadone; at present, the drug is usually given short term to detoxify small numbers of inmates in some prisons. The effectiveness of maintenance regimens administered in prison needs to be evaluated, but it seems sound to develop this approach.

Needle and syringe sharing remains a problem in community and prison settings. In the community, sharing is driven by convenience; in prisons, by need. Since injectors frequently move in and out of prison, any major discordance between the effectiveness of prevention strategies in prison and in the community will allow the spread of HCV to continue unabated. Only a coordinated approach to harm reduction can succeed.

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