Clinical Review

Clinical Review indentifies issues in the medical literature of interest to clinicians in Africa. Essential references are given at the end of each section

AIDS Review

'The world is in recession, but HIV/AIDS is not in recession,' so blasted the trumpets from activists, scientists, and people affected with HIV/AIDS at the 5th International AIDS Conference on HIV Pathogenesis, Treatment and Prevention at Cape Town, South Africa, in July 2009. The perceived backlash against HIV/AIDS and the threatened withdrawal of international support for HIV/AIDS as well as for other disease-specific programmes was defiantly confronted by the 7000 or so delegates, justifiably angry at the way governments worldwide seem able to find billions of dollars to support failing banks but unable to find a few billion to save the lives of people affected with HIV/AIDS, tuberculosis (TB), and malaria in some of the poorest countries of the world.

'Towards Universal Access'

The September 2009 Progress Report on the scaling-up of HIV/AIDS interventions in the health sector acknowledges the continuing challenge that the HIV epidemic poses for global health, with 33 million adults and children living with HIV and 2.7 million new infections in 2007.[1] Nevertheless, despite the challenges and the shortfalls in the global response to the epidemic, undoubted progress has been made.

At the end of 2008, more than 4 million (3.7–4.4 million) people were receiving antiretroviral therapy (ART) in low- and middle-income countries, an increase of more than 1 million compared with the end of 2007 and a 10-fold expansion in 5 years. The greatest increase has been in sub-Saharan Africa where about 2.9 million (2.7–3.2 million) people were receiving ART at the end of 2008. The estimated coverage of ART in low- and middle-income countries reached 42% and coverage in sub-Saharan Africa was 44%. About 60% of adults receiving ART in reporting countries were women, who represent 55% of the people in need. In 2008, 38% (31%–47%) of children estimated to need ART globally had access. In sub-Saharan Africa, between 2007 and 2008, the estimated number of children receiving ART increased from 158 000 to 225 000, with total coverage in children reaching about 35%. Retention on therapy is of concern, with rates reported at 75% at 12 months and 67% at 24 months. Most of the attrition occurs early, in the first year of treatment, reflecting the fact that many people living with HIV (PLHIV) present late and die during the first few months of treatment. TB continues to be a leading cause of death in PLHIV. There were an estimated 1.37 million HIV-infected TB cases in 2007, of whom 456 000 died during anti-TB treatment.[2] Collaborative HIV and TB activities need to improve. For example, in 2007, only 16% of notified TB patients knew their HIV status and only 100 000 (7.3%) co-infected TB patients were believed to have started ART, figures that are in desperate need of improvement to avert HIV- and TB-related deaths.

Access to services for preventing mother-to-child transmission in low- and middle-income countries continued to expand in 2008. Twenty one percent of pregnant women received an HIV test in 2008, up from 15% in 2007, and 45% of HIV-infected pregnant women in the region received antiretroviral drugs to prevent mother-to-child transmission, up from 35% in 2007.[1] However, early infant diagnosis remains problematic, and in 41 reporting countries only 15% of children born to HIV-infected mothers were tested for HIV in the first 2 months of life.

The availability and uptake of HIV testing and counselling continued to increase in 2008. In 66 low- and middle-income countries with comparable data, the total number of health facilities providing HIV testing services increased from 25 000 in 2007 to 33 600 in 2008.[1] Population-based surveys conducted between 2005 and 2008 showed that the proportion of people ever tested for HIV increased from 15% to 39%, largely as a result of provider-initiated HIV testing and counselling in healthcare facilities.

New data on epidemiology and dynamics of the HIV epidemic in Africa

A recent review in the *Lancet* indicated the widespread existence of men who have sex with men (MSM) groups in sub-Saharan Africa and high rates of HIV infection.[3] However, because homosexuality is illegal in many countries and political and social hostility is endemic, the challenges in providing relevant HIV/AIDS information and services are huge, but nevertheless need to be tackled if headway is to be made.

Many African countries with high HIV prevalence and low rates of male circumcision established policies in 2008 to scale-up male circumcision, although hard data on actual progress is difficult to find. Disappointingly, a well-conducted study in Uganda showed no reduction in risk of HIV transmission to female partners of HIV-infected men who had been circumcised,[4] challenging previous observational studies reporting an association between male circumcision and reduced HIV infection in female partners. Although providing no direct benefit for the women, it is likely that women will benefit from male circumcision programmes as wide scale roll-out would lead to decreasing HIV prevalence in communities over 10–20 years.

Universal HIV testing and immediate start of ART

Despite current best efforts, the annual number of new infections remains high and continues to outpace the number of people receiving ART. In January 2009,

a radical approach was presented in the *Lancet* to controlling the HIV epidemic in high burden areas of sub-Saharan Africa.[5] Using a mathematical model that included the case reproduction number (stochastic model), long-term dynamics of the HIV epidemic (deterministic transmission model), and data from South Africa as representative of a generalised heterosexual epidemic, a strategy was proposed of testing all adults for HIV every year and starting ART immediately after they are diagnosed HIV-positive. The authors claimed that this could reduce HIV incidence and mortality by 95% in 10 years, and HIV prevalence to less than 1% within 50 years. The conclusion was that this approach merits further mathematical modelling, research, and broad consultation.

Not surprisingly, this proposal has caused a huge amount of discussion and controversy, not least of which is the argument that ART would be for public-health benefits rather than individual patients' benefits, particularly if the costs of toxicity and inconvenience outweigh the clinical benefits.[6] In this regard, two large observational studies were published during 2009 from the industrialised world examining the benefits of early versus deferred ART on individual survival.[7,8] Both articles, examining a total of almost 40 000 HIV-infected patients from the USA and Europe, found that starting ART at CD4 counts of 350 cells/µL or higher was associated with a significant reduction in risk of death. This provides evidence that there is individual benefit to early ART start. The model of universal HIV testing and immediate start of ART needs to be taken seriously, and tested for efficacy, feasibility, safety, impact, and cost, with attention paid to operational aspects such as community acceptability, protection of human rights, safety, and acceptability of ART regimens, quality delivery systems and effective monitoring and reporting.

HIV vaccines

There was a seminal publication in October 2009 of a randomised controlled efficacy trial in Thailand evaluating a prime-boost HIV vaccine in 16 402 healthy men and women.[9] ALVAC HIV was the prime vaccination (consisting of a canarypox viral vector and genetically engineered versions of HIV *env*, *gag*, and *pro* genes, and designed to elicit a T-cell-mediated response). AIDSVAX B/E was the boost vaccine (consisting of recombinant gp120 spike proteins derived from HIV subtypes B and E, and designed to induce antibody-mediated immunity). Immunisation required six injections over 6 months, four with ALVAC HIV and two with AIDSVAX B/E at the same time as the last two ALVAC HIV injections. In a modified intention to treat analysis there was a relative reduction of infection of 31.2% (95% confidence interval (CI), 1%–51%) in vaccine recipients. Vaccination did not affect the degree of viraemia or the CD4 cell count in those in whom HIV-1 infection was subsequently diagnosed.

For those working or keeping up-to-date with vaccine trials, this was a surprising result as the two vaccine candidates, when evaluated independently, had performed poorly in previous clinical trials. Many questions also remain as to the wide confidence intervals around efficacy, the duration of efficacy, the protective effects in high-risk groups, and whether this vaccine geared towards the HIV B and E subtypes that circulate in Thailand would be appropriate in other settings, especially in Africa where subtype C reigns supreme. Nevertheless, it is the first of the HIV vaccine studies that offers a glimmer of hope in a field previously littered with disappointments.

Linking HIV/AIDS support with health systems

The debate and discussion continues about the relative merits of supporting disease-specific programmes such as HIV/AIDS or primary healthcare systems, although perhaps with less polarisation than 12 months ago. The US President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) are major global health initiatives that have transformed the landscape of global health.[10] Richard Horton, Editor of the *Lancet,* argues eloquently that these financing initiatives now need to broaden their mission and include additional health goals such as maternal, newborn, and child health.[10] This has to be the right approach so that we move towards 2015 knowing that globally we are pooling and committing our resources to tackle the three important health-related Millennium Development Goals, MDG 4,5, and 6.

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Medicine Review

Strongyloidiasis

A recent review article in the *Transactions of the Royal Society of Tropical Medicine and Hygiene* draws attention to the rather forgotten condition of strongyloidiasis – human infection with the nematode work – *Strongyloides stercoralis*.[1] This is a soil-transmitted helminth – part of a group of infections which are on the accepted list of 'neglected tropical diseases'. Indeed, the authors refer to strongyloidiasis in the title of their article as 'the most neglected of the neglected tropical diseases'.

Strongyloidiasis is widely distributed in the tropics and sub-tropics, and also occurs in some temperate zones. The worm is highly advanced, with life cycle adaptions to help survival. There is a free-living sexual cycle in the soil, which can persist without the need for human infection. Soil larvae can, however, infect man by penetration of intact skin (usually of the feet). Filariform larvae travel to the lungs, migrate up the bronchial tree and are swallowed. In the duodenum and proximal jejunum, the larvae develop into adult females which produce eggs. These eggs develop into rhabditiform larvae, which are passed in the stool from where they enter the soil and the free-living cycle. However, rhabditiform larvae can 'auto-infect' the human host by penetrating the rectal mucosa or peri-anal skin. These larvae then migrate to the lungs, to continue the human cycle without the need for new external infection. The process of auto-infection explains why strongyloidiasis can continue indefinitely even when infected patients move out of areas of endemic infection. This has important implications for travellers in the tropics who return to their homes in temperate regions.

The clinical presentation of *Strongyloides* infections is highly variable, and many infections can be quite asymptomatic. Acute infections can cause diarrhoea and/or abdominal pain. Occasionally the diarrhoea can be bloody ('dysenteric strongyloidiasis'), and sometimes may become long-standing and associated with malabsorption and weight loss (a 'sprue-like' syndrome). In chronic auto-infective infections, abdominal symptoms are less common, and a more frequent feature is the 'larva currens' rash, sometimes known as 'creeping eruption'. This represents the migration of auto-infecting larvae, and consists of an urticarial wheal surrounded by an erythematous flare, which rapidly moves around the central body areas (trunk, shoulders, or buttocks). The rash comes and goes, often with weeks or months between attacks.

A final, but very serious, clinical manifestation of strongyloidiasis, is known as 'hyperinfection'. If an infected host suffers immune suppression (of any cause – but steroid drug treatment is the most common), then larvae can migrate outside the bowel to the peritoneum, liver, lungs, and central nervous system. Patients often present with Gram-negative septicaemia and shock. Diagnosis is often missed and the mortality is high.

Because the presentation of strongyloidiasis is so variable, a high degree of diagnostic suspicion is needed. Demonstration of typical larvae on stool microscopy confirms the diagnosis, but larval excretion is often intermittent and even three negative stool examinations does not exclude the diagnosis. Blood eosinophilia is often present, and if available modern ELISA or PCR serological tests are helpful. The treatment of choice is now ivermectin 200 µg/kg (either single treatment, or daily for 3 days). Alternatively, albendazole (400 mg twice daily for 3 days) can be used. Treatment of the hyperinfection syndrome is difficult – full supportive treatment including fluids, antibiotics, etc should be given, as well as anthelmintic drugs as above. Sometimes, however, there is intestinal ileus and oral drugs cannot be given. A veterinary preparation of ivermectin is available sometimes, and a single subcutaneous dose of 12 mg has been reported to have been successful. As mentioned, strongyloidiasis can occur in temperate zones. There is low-grade endemicity in the southern states of the USA, and some parts of Europe. In Britian, chronic auto-infective *Strongyloides* infections have been especially diagnosed in former Far East prisoners of war (POWs) of the Japanese during World War II. These infections usually started in the prison camps of the Thailand jungles and have persisted for decades afterwards in the UK. Two occurrences of fatal hyperinfection have been recorded in this group of men.[2]

The message for doctors in Africa is to increase awareness of this variably presenting infection. More widespread use of mass treatment for soil-transmitted helminths will help with control, as will encouragement of the use of footwear (especially in highly prelevant areas). Patients who are likely to need steroid drugs (for example asthmatic patients) should receive particular attention – probably with annual albendazole, or regular stool microscopy.

Neuroschistosomiasis

Strongyloides stercoralis is not the only worm that can persist long-term in infected hosts who have left the endemic area. A recent case report concerns a South African man who presented with *Schistosoma mansoni* infection over 20 years after likely exposure (the patient had moved to New Zealand).[3] He presented with acute urinary retention and sensory signs and symptoms in his legs. He had a past history of urinary schistosomiasis as a child. Investigations showed a cerebrospinal fluid (CSF) lymphocytocis, swelling of the conus medullaris on magnetic resonance imaging (MRI) scanning, strongly positive schistosomal serology, and eggs of *S mansoni* in the faeces. A diagnosis of schistosomal myeloradiculopathy was made and he was treated with high-dose intravenous methylprednisolone for 5 days with oral praziquantel for the first 2 days. Sensory symptoms initially worsened and he was given a further course of intravenous steroids, following which he improved and eventually made a complete recovery.

Schistosomiasis has been previously reported as surviving for up to 30 years, and a distant travel history is important if the diagnosis of infection is to be considered. The case also demonstrates the importance of neurological presentations of this condition. Eggs can reach the spinal cord either by embolisation, or due to migration of adult worms. In many developing countries,

MRI scanning and efficient serological tests are not available. Eggs may not be present in the stool, and the diagnosis may have to be clinical. In areas of high endemicity, patients presenting with cord syndromes (especially urinary retention and/or neurological signs and symptoms in the legs) for no obvious cause, should be considered as having potential neuroschistosomiasis.

Prompt treatment is vital, as otherwise permanent neurological damage may result. Praziquantel is the drug of choice, but steroids must also be used to reduce cord swelling.

Tight blood pressure control

Hypertension is very common in Africa, and is a major risk factor for stroke. It is known that adequate treatment of hypertension reduces the risk of stroke and other complications, but it is not certain what ideal 'target' blood pressure (BP) levels should be for those on treatment. In type 2 diabetes, there is now very good evidence that tight BP control (systolic BP <130 mmHg) greatly improves outcome in terms of morbidity and mortality. A study has recently been published which suggests that the same applies for non-diabetic patients.[4]

The study was a randomised multi-centre study from Italy of 1111 non-diabetic adult hypertensive patients. They were randomised to have their systolic BP lowered to <140 mmHg (standard control) or <130 mmHg (tight control). Patients were followed for 2 years, and as this was too short a period to assess mortality effects, the main endpoint was electrocardiographic (ECG) left ventricular hypertrophy (LVH). This occurred in 17.0% of those on standard control, and 11.4% of those on strict control (p=0.013).

Clearly, this was not a long-term outcome study, but nevertheless it lends strong support to the beneficial effects of strict BP control in non-diabetic as well as diabetic hypertensive patients. A target of <130/80 should now be regarded as ideal.

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Paediatrics Review

Enterobius vermicularis: not always benign

Enterobius vermicularis (EV) is an extremely common gut parasite which is usually asymptomatic or may cause mild perianal irritation and pruritus. Peak prevalence rate is at 5–9 years. It is considered to be more common in temperate than tropical areas. Possible reasons include infrequent washing and change of underclothes in lower socio-economic groups, especially in winter.

When EV ova are ingested the larvae are released from the eggs by digestive enzymes in the duodenum and the adult worms move to the distal ileum, caecum, and ascending colon where they mate.[1] The gravid female worms migrate towards the ano-rectal region and lay their eggs on the perianal skin usually at night and die within a few hours. The life cycle is completed through auto-infection by contaminated fingers or fomites or when larvae migrate back into the rectum and gastrointestinal tract where they mature and mate.

Complications arise from granulomatous reaction to the eggs or worms which are lodged in ectopic sites. In girls they may be associated with urinary tract infection and vaginal discharge. In adolescent girls and women the worms may migrate up the genital tract and cause disease of the vulva, vagina, uterus, and fallopian tubes resulting in salpingo-oophoritis.[2–5] The worms may reach the peritoneum and produce chronic inflammation and pelvic pain or a generalised peritonitis. Access to the genital tract for EV explains why disease due to ectopic worms is more common in females.[2]

Other ways the worms may reach the peritoneum are through a perforated appendix or bowel,[6] during surgery or because of carcinoma.[3] The liver, spleen, and kidney may be affected by migration of the worms in the peritoneum. EV is detected in around 2% of appendices excised electively or for appendicitis.[7]

One of the commonest serious complications is enterocolitis.[6,8] Usually this is associated with heavy infection by EV. Damage to the gut mucosa due to coincidental infection may allow EV larvae or immature worms to invade the bowel wall.[1,9] Involvement of the ileum and the proximal colon may produce symptoms and colonoscopic features of inflammatory bowel disease (IBD).[9] Involvement of the proximal small intestine has resulted in malabsorption syndrome; the thickened bowel wall was detected on both barium meal and CT scan.[10] Other reports have also documented CT evidence of thickening of the walls of the ileum and caecum associated with EV infection. Histology demonstrated intense eosinophilic infiltration. Another report described gangrenous jejunum with mesenteric nodes and transmural eosinophil and polymorphonuclear infiltration on histology.

Additional ectopic sites for EV include the lungs, presumably through embolic blood spread, or through migration down the trachea,[2] and cerebrospinal fluid (CSF). Direct contamination of the external auditory meatus, nasal mucosa and conjuntiva, presumably by fingers contaminated by EV larvae, is described. An allergic rash which responded to treatment of EV has also been reported.[10] Interestingly, despite the peak prevalence of EV being in the pre-pubertal period most of the serious complications have been described in adults. Although this is likely to be due to its predominance in

women, it could also possibly be due to an exaggerated hypersensitivity reaction to ova/worms in ectopic sites which might be more likely to occur in adolescents and adults in whom the immune system is more mature than in younger children.

A report from Alder Hey Children's Hospital, Liverpool has increased our knowledge about intestinal disease related to EV in children.[11] A retrospective study of all children in whom colonoscopy was performed over a 3-year period is described. Most of the patients presented with symptoms suggestive of IBD, particularly rectal bleeding. Of 180 patients, EV was detected in 31cases (17.2%) and complete data were available for 21 of these. Symptoms had been present for a time period ranging from 2 weeks to 5 years. No patient had perianal symptoms. Only two had a peripheral eosinophilia. In 20 patients from whom a saline rectal swab was taken, all were negative for EV. In 21 of the 26 patients there was histological evidence of non-specific colitis, *vis*, shallow mucosal ulcerations with segmental subepithelial haemorrhages, eosinophil infiltration, and mild focal inflammation. All were treated with mebendazole and 83% had a clinical response over a follow up period of 1–5 years. None of the patients developed IBD.

As EV is such an ubiquitous intestinal helminth the detection of worms in the gut or eggs on the anus may be coincidental, thus histological evidence is important. In ectopic sites necrotic ova are detected more often than the female worm but an ectopic gravid worm is likely to cause a larger immunological reaction.[2] There is usually evidence of a chronic granuloma with variable numbers of plasma cells, histiocytes, lymphocytes, eosinophils, and foreign body giant cells with surrounding fibrosis.[2] Eosinophils are the most constant feature. Blood eosinophilia is common but is not necessary for the diagnosis. For detection of intestinal infection, worms may be seen on proctoscopy or colonoscopy, however, this depends on the experience of the endoscopist and also on the level of infection. Saline rectal swabs may be used or adhesive tape may be applied to the anus in the morning. If the latter is done once, the positivity rate is only 5–10%; this rises to over 90% if the procedure is undertaken for 5 consequtive days.[1] Ova may also be detected from swabs taken from under the fingernails of patients.

Response to treatment (albendazole 400 mg or mebendazole 100 mg, one dose repeated in 2 weeks) is important for confirmation of the diagnosis. However, EV infection of the female genitals may be associated with infertility and chronic pelvic pain despite treatment.[4,5]The latter may be a form of autoimmunity, where there is on-going reaction to the dead ova/worms, and may require drugs for immune modification.[5]

Dientamoeba fragilis is a flagellate which was first described in 1918. It is associated with acute or chronic gastrointestinal symptoms including abdominal pain, persistent diarrhoea, allergic colitis, flatulence, anorexia, and weight loss.[12] Because it has no resistant cystic stage it is considered that the trophozoites are unlikely to exist outside the human host. It is thought that transmission may occur via the ova of EV. Thus, this parasite could in some circumstances be responsible for some of the symptoms associated with EV. However, more investigation is required to substantiate this theory.

In conclusion, EV can sometimes cause more than anal pruritus. Unfortunately, it has low priority for research in both developing and industrialised countries. Prospective studies are required to investigate the role of EV in non-specific colitis in children and also its association with *D fragilis*. In adolescent girls and women EV should be considered in the aetiology of chronic pelvic pain. In those in whom EV is demonstrated to be the likely cause, and in whom neither antiparasitic treatment nor surgery is of benefit, the role of immune modification treatment should be considered.[5]

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