Clinical Review

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

AIDS Review

The year 2011 will be remembered for a landmark trial that showed conclusively that early antiretroviral therapy (ART) given to HIV-infected persons can prevent HIV transmission to uninfected partners or spouses,[1] and 'treatment for prevention', as it is termed, will undoubtedly shape the future of our response to the AIDS epidemic. 2011 was also a landmark year – it marked 30 years since the first reported cases and the official start of the HIV/AIDS epidemic, 15 years since combination treatment became a reality, 10 years since the United Nations General Assembly Special Session on HIV/AIDS, and 5 years since the Joint United Nations Programme on HIV and AIDS (UNAIDS) and the World Health Organization (WHO) committed to achieve universal access to HIV prevention, treatment, care, and support.[2] Both WHO and UNAIDS have developed forward-looking strategies to support countries in their efforts to combat the disease and achieve the Millennium Development Goals, with a number of concrete objectives and targets that can be summed up under the 'three zeros' – zero new HIV infections, zero discrimination, and zero AIDS-related deaths.

Epidemiology of HIV/AIDS

The 2011 UNAIDS report provides the latest figures.[3] An estimated 30 million people have died of AIDS-related causes since the first case of AIDS was recognised in June 1981. By the end of 2010, there were an estimated 34 million people living with HIV globally, with 2.7 million new infections and 1.8 million AIDS-related deaths occurring in that year. New infections are 21% less than at the peak of the epidemic in 1997, and deaths are down from a peak of 2.2 million in the mid-2000s. Sub-Saharan Africa continues to bear the brunt of this epidemic with 22.9 million people living with HIV (67% of global total), 1.9 million new infections (70% of global total), 1.2 million AIDS-related deaths (67% of global total), and an adult HIV prevalence of 5%. There is considerable variation in the severity of epidemics on the continent, with southern Africa still the most severely affected region, and South Africa's epidemic the largest in the world.

HIV treatment and Treatment 2.0

At the end of 2010, about 6.6 million people were receiving ART in low- and middle-income countries, and a record 1.4 million people started this life-saving treatment in 2010 – more than in any year before.[3] A study from Uganda showed that HIV-infected patients receiving ART could expect an almost normal life expectancy, with nearly 27 years of additional life for those starting at 20 years of age, although this was highly dependent on the baseline CD4-lymophocyte count at which ART was commenced.[4]

Despite expanded access to ART, at the end of 2010, 9 million people eligible for treatment did not have access – coverage rates being 36% for people of all ages and 28% for children. A synthesis of findings from multiple studies in sub-Saharan Africa suggested that less than a third of patients testing positive for HIV and not yet eligible for ART are retained continuously in care, with significant drop-offs occurring at all stages: 41% drop-off from receipt of HIV testing to receipt of CD4 count results or clinical staging; 54% drop-off from staging to ART eligibility; and 32% drop-off from ART eligibility to ART initiation.[5] Much better systems are needed to track patients between service delivery points and in particular to ensure rapid linkage of HIV testing results to HIV care and treatment.

In this regard, WHO and UNAIDS's new "Treatment 2.0" might help to address these deficiencies.[6] It is designed to maximise the efficiency and effectiveness of HIV treatment through a focus on five priorities.

1. Optimising drug regimens through one-pill-per-day formulations, simplified process chemistry, and dose reductions.
2. Advancing point-of-care and other simplified platforms for diagnosis and monitoring, especially for CD4-lymphocyte counts and viral load.
3. Reducing costs through commodity price reductions, use of market and trade flexibilities and efficiency gains across HIV programmes.
4. Adapting delivery systems through decentralisation and integration.
5. mobilising communities to create demand, to participate in the design and implementation of services, and to promote and protect human rights.

Point-of-care CD4-count testing is already becoming a reality. An operational research study in Mozambique showed that the introduction of this technology at primary health clinics reduced pre-treatment ART loss to follow-up from 64% to 33%, the median time from enrolment to ART initiation from 48 days to 20 days, with the most substantial reduction being the median time between enrolment and CD4 staging which decreased from 32 days to 3 days.[7] Treatment 2.0 also serves as the crucial platform to move forward on 'treatment for prevention'.

Treatment for prevention

Previous observational cohort studies have strongly suggested that ART is an important means of reducing HIV transmission, but the HPTN (HIV Prevention Trials Network) 052 multi-continent, randomised controlled trial which was published in August 2011 provides the Grade 4 evidence.[1] The study enrolled 1763 discordant couples in which one partner was HIV-1 positive and the other was HIV-1 negative. HIV-infected subjects

had CD4 counts between 350 and 550 cells per mm^3, and were randomly assigned to receive ART either immediately (early therapy) or after a decline in the CD4 count to 250 cells per mm^3 or less or the development of AIDS (delayed therapy). During the study, there were 39 HIV-1 transmissions, of which 28 were virologically linked to the infected partner. Of the 28 linked transmissions, only one occurred in the early therapy group, a 96% attributed reduction in HIV transmission. This study paves the way for the use of ART as part of a public health strategy to reduce the spread of HIV infection.

Malawi, a small country in southern Africa, has already moved on to using this approach for prevention of mother-to-child transmission of HIV.[8] WHO currently recommends two approaches for HIV-infected pregnant women who do not need ART for their own health, i.e. women with CD4 counts > 350 cells per mm^3: Option A or Option B, the latter being ART for the pregnant woman and continued until the end of breast feeding at which point it is stopped. Malawi has made a policy change to offer HIV-infected pregnant women lifelong ART regardless of CD4 count (branded Option B+), recognising that the total fertility rate in the country is high and the fact that most women become pregnant again soon after the end of their breast-feeding period (which lasts a median of 23 months). This should have several treatment and prevention benefits, and other countries are now considering whether to also adopt this strategy.

ART for preventing tuberculosis

One of the additional benefits of early ART is prevention of tuberculosis (TB). TB remains a scourge in HIV-infected people, especially in sub-Saharan Africa. In 2010, there were an estimated 1.1 million incident cases of TB among the 34 million people living with HIV, of whom 350 000 died.[9] Over 80% of these incident cases occurred in sub-Saharan Africa, and the deaths were largely because of unrecognised TB in HIV-infected persons, unrecognised HIV in TB patients, and late presentation. Strategies to prevent TB in HIV-infected people include the 'Three I's' (intensified tuberculosis case finding, isoniazid preventive therapy, and TB infection control) and ART. In recent years, accumulating evidence has pointed to the potential of ART scale-up to contribute further to the control of HIV-associated TB, by reducing the risk of new incident TB, recurrent TB, and mortality. Currently, however, the initiation of ART at low CD4 cell counts (by which time much HIV-associated TB has already occurred) and low effective coverage greatly undermine the potential preventive impact at a population level. Mathematical modelling and a keen understanding about the critical components of HIV that drive the TB epidemic strongly support a shift towards initiation of ART at much higher CD4 counts than is currently happening.[10]

The funding conundrum

Progress is being made in the fight against HIV/AIDS, with scientific advances, scale-up of interventions known to work (such as male circumcision), political support, and community responses starting to deliver clear, concrete results. Much of the success has come in the last 2 years. At the end of 2010, US$15 billion was spent on the response to HIV/AIDS, with low- and middle-income countries contributing just half that total. The money is not enough, and UNAIDS estimates that over US$20 billion is needed to support the bold ambitious plans, that if implemented to scale, would make a significant dent in the epidemic.

However, all is not well. Worrying trends in funding were already apparent 1 year ago when international funding fell from US$8.7 billion in 2009 to US$7.6 billion in 2010. The cancellation in November 2011 of the Global Fund Round 11 due to lack of resources is cause for real alarm. This is an unprecedented act in the history of the Global Fund. It comes at a pivotal time when evidence shows that ART can save lives as well as prevent the spread of HIV, and when UN agencies and governments are talking about a possible end to the epidemic. History will judge us harshly, and rightly so, if we let the opportunities currently in our grasp slip from our hands because of insufficient money.

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Paediatrics Review

Fluid bolus for impaired perfusion in children with sepsis

In high-income countries where intensive care facilities (inotropes and ventilatory support) are available, common practice for treatment of shock is to give up to 60 ml/kg of isotonic fluid within 15 minutes after diagnosis of septic shock.[1] World Health Organization guidelines only recommend fluid bolus in children

without severe malnutrition for advanced shock, i.e. delayed capillary refill >3seconds, weak and fast pulse and cold extremities; where appropriate, fluid bolus should be given as 'rapidly as possible', repeated twice if necessary.[2]

The Fluid Expansion as Supportive Therapy (FEAST) study investigated the value of bolus treatment for septic shock in low-income countries in the expectation that it would improve outcome.[3] The study design comprised 0.9% sodium chloride vs no bolus (control) and 5% albumin vs saline bolus in children (aged 60 days–12 years, median 24 months) with severe febrile illness complicated by impaired consciousness, respiratory distress, or both, and impaired perfusion (Group A). Impaired perfusion was defined as one or more of the following: capillary refill ≥3 seconds, lower limb temperature gradient, weak radial pulse volume, or severe tachycardia.Those with acute severe malnutrition (defined as visible severe wasting or kwashiorkor), gastroenteritis and non-infectious causes of shock, e.g. trauma, burns) were excluded. Those with severe hypotension (decompensated shock) were given either albumin or saline bolus (Group B). Fluid rates were as follows. Group A, 20 ml/kg over 1 hour and repeat 20 ml/kg bolus at 1 hour if impaired perfusion persisted; Group B received 40 ml/kg and an additional 20 ml/kg at 1 hour if necessary.

The study commenced in January 2009. Study sites were in six hospitals in Uganda (4), Kenya (1), and Tanzania (1). In June 2010 the initial bolus volume was increased to 40 ml/kg for Gp A and 60 ml/kg for Gp B. In patients with Hb <5 g/dl, 20 ml of whole blood was transfused over 4 hr. Adverse events such as pulmonary oedema and increased intracranial pressure were recorded but the method of diagnosis was not given.

Based on an estimated 15% risk of death in the control group, the initial sample size of Group A was 2800. In June 2010, because of lower than expected mortality, the sample size was increased to 3600. However, the study was stopped in January 2011 after recruitment of 3141 patients because of an excess of deaths in the bolus compared with the control group of 3.3% and the risk of death, neurological sequelae, or both, at 4 weeks of 4.0%.

Results

Only 29 patients were enrolled in Group B and mortality was 69% in the albumin group, and 56% in the saline group (p=0.45). In Group A (3141 patients), 57% had malaria and 4% HIV infection. Common clinical features amongst the three study groups were prostration (62%), coma (15%), respiratory distress (83%), moderate–severe acidosis (51%), severe lactic acidosis (39%), and oxygen (O_2) saturation <90% (25%). A third of patients (1070) underwent a blood culture and in 12% it was positive. However, a final diagnosis of cause of infection was not reported. Mortality was lower in patients with severe malaria than in the subgroup without malaria but this was not related to any difference in bolus therapy. Hb <5 g/dl was detected in 987 (32%) patients. Mean (SD) Hb was 7.1 (3.2 g/dl). Hb <5 g/dl was detected in 15.4% of the bolus compared with 9.0% of the no bolus group (95% confidence interval (CI), 1.71 (1.16–2.51). A total of 1408 patients received a blood transfusion (43–47% of the three study groups). Blood transfusion was given slightly earlier in the control group but by 2 hours the proportion of patients who received blood and the volume was similar across the three study groups. Mid-upper-arm circumference of <11.5 cm was 2% in each of the three groups. Over the course of 8 hours the median cumulative volume of fluid (ml/kg) was as follows: albumin bolus, 40; saline bolus, 40; and control, 10.

Mortality at 48 hours

Eight-seven per cent of the deaths occurred before 24 hours. Risk of death in the first hour was similar between the three groups but thereafter there was a persistent trend for increased mortality in the bolus groups. By 48 hours deaths were as follows: albumin bolus, 10.6%; saline bolus, 10.5%; and control, 7.3%; p values for differences between the following groups were: saline vs no bolus (p=0.01), albumin vs no bolus (p=0.008), albumin vs saline (p=0.96), and albumin + saline vs no bolus (p=0.003). The excess of deaths in the bolus groups was consistent across a wide number of subgroups including physical signs, O_2 saturation, and laboratory values.

Comment

In high-income countries, rapid fluid bolus is regarded as essential for the treatment of shock in children.[1,4] However, the optimal type of fluid is still debated. A systematic review of use of albumin for resuscitation in critically ill patients found no evidence that albumin reduces mortality compared with cheaper alternatives such as saline.[5] A systematic review of clinical trials comparing crystalloids and colloids for fluid resuscitation in children with severe infection in low-resource countries was unable to recommend any fluid as superior to others.[6] However, in a randomised trial comparing fluid resuscitation with albumin or saline for treatment of children with severe malaria and acidosis, mortality was lower in the albumin (3.6%) compared with the saline group (18%) (p=0.013).[7] There was no difference in resolution of acidosis.

The FEAST trial was a well conducted study with adequate sample size.[8] The study patients would have, in general, differed in their pre-admission state of health compared with similar children in high-income countries where intensive care facilities would also be available. Thus, practices in high-income countries may not necessarily always be suitable for some sick children in low-income countries endemic for severe malaria. Although no single factor could be isolated to explain the higher mortality in the bolus groups, in a subgroup of patients a combination of factors might have made some children from poor communities vulnerable to fluid overload. These include occult nutritional deficiency, e.g. zinc, impaired cardiopulmonary function and hypoxia (due to anaemia and/or pneumonia), raised intracranial pressure (due to bacterial meningitis, cerebral malaria or encephalopathy), all of which are associated with increased fluid retention due to raised levels of

antidiuretic hormone (ADH),[9] or borderline serum albumin levels which in the presence of raised inflammatory cytokines might exacerbate capillary leak. In addition, the question arises as to whether all the patients had impaired perfusion sufficient to warrant a large bolus of fluid. The diagnosis of impaired perfusion was based on one or more of the signs of shock rather than a combination of signs as defined in the WHO criteria.[2] Some of the signs of shock are non-specific and if used singly may over-diagnose impaired perfusion.[9,10]

Based on the results of the FEAST trial it is recommended that the present policy of rapid fluid-bolus resuscitation in children with febrile illnesses and compensated shock should now be revised, or at least, undertaken with much greater caution.[8] However, further analysis of this study is required before the current practice for treatment of shock in children in high-income countries is reversed.

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Medicine Review

Cardiovascular risk and ARVs

It has been known for some time that antiretroviral (ARV) therapy can increase cardiovascular risk. There are various possible mechanisms, but perhaps the best known is the effect of protease inhibitors in leading to central obesity (the 'protease paunch'). This can lead to a fatty liver, dyslipidaemia, insulin resistance, hypertension and impaired glucose tolerance (including overt diabetes). With the now widespread use of ARVs in Africa, this problem is set to become of increasing importance. Programmes to reduce or control other cardiovascular risk factors may become necessary.

Researchers from Malawi (where there are currently approximately 225 000 patients receiving ARVs) have recently published work investigating cardiovascular risk factors in a group of ARV-treated patients.[1] They studied 174 adults who had been on ARVs for at least 12 months, from the Queen Elizabeth Central Hospital in Malawi. A questionnaire was used to record information on smoking, diet, and exercise. Blood pressure (BP), body mass index (BMI), waist–hip ratio (WHR), and serum cholesterol were also measured.

The mean age of the group was 41 years and 61% were female. The mean duration of ARV treatment was 35 months. Smoking was uncommon (0.6%), but 68% had a diet considered not ideal (usually insufficient fruit or vegetables). Only 19% undertook regular physical exercise. Most patients were lean with a mean BMI of 22.7 kg/m^2, but WHR (as a measure of central obesity) was raised in 45%. Hypertension was common, with 46% having a BP level over 140/90 mmHg. The mean random blood glucose (RBG) level was 4.6 mmol/l, with only 2 patients (1.2%) having an RBG in the diabetic range of >11.1 mmol/l. Mean serum cholesterol was 4.4 mmol/l, with 31% having a level over 5.0 mmol/l.

Ideally a full fasting lipid profile and glucose tolerance test would have been preferable to the RBG and serum cholesterol levels measured. This may have revealed more subtle patterns of dyslipidaemia and glucose tolerance. Nevertheless, the study is welcome and useful, as it shows significant issues with inadequate diet and exercise patterns, as well as frequent hypertension and central obesity. Though the study itself was not controlled, the researchers were able to compare most results with recently collected information from the general Malawian population; and hypertension, hypercholesterolaemia, and low exercise levels did appear more common in the ARV-treated patients.

These results are of concern, and suggest that there is a case for routine screening for cardiovascular risk factors in patients on ARVs, as well as an education programme on diet and exercise. Regular BP monitoring and vigorous treatment of hypertension is also likely to be highly beneficial.

Type 2 diabetes – the sugar connection

The connection between good blood glucose control and outcome in type 2 diabetes has always been controversial, as opposed to type 1 diabetes where the relationship is much more certain. In the landmark UKPDS (United Kingdom Prospective Diabetes Study),[2] which compared large groups of patients with 'tight' and 'moderate' glycaemic control, there was a definite improvement in microvascular complications outcome with tight control, but no definite benefit for large vessel disease (the main cause of deaths in type 2 diabetes). Lipid and blood pressure control, however, have a much stronger evidence-base for outcome benefit in type 2 diabetes, and are easier to deliver than intensive blood glucose control.[3] In addition, a recent trial – 'ACCORD' (Action to Control Cardiovascular Risk in Diabetes) – has shown an increased mortality in particularly 'tightly' controlled type 2 patients (particularly with an HbA_{1c} <6.5%).[4] It has been suggested that hypoglycaemia-induced cardiac events may have contributed to this

mortality problem, though the exact reason remains uncertain.

These issues are important, as they greatly affect the debate on what the ideal glycaemic target for treatment in type 2 diabetes should be. It seems that 'the lower the better' (generally accepted in type 1 diabetes) may not be the case in type 2 disease. Alternatively, is there a reasonable target to help improve microvascular outcomes, but below which there may be adverse mortality effects? A recent meta-analysis by Dutch researchers has helped to clarify the situation by examining the combined results of 14 clinical trials examining the effect on outcome of intensified blood glucose control in type 2 diabetes.[5]

The 14 trials involved 28 614 patients with type 2 diabetes, of whom 15 269 had received intensive glycaemic control, and 13 345 conventional control. The relative risk (RR) of all-cause mortality was not significantly affected by intensive control (RR 1.02, 95% confidence intervals (CI) 0.91–1.13). Cardiovascular mortality was similarly unaffected (RR 1.11, 95% CI 0.92–1.35). Intensive control did reduce the risk of retinopathy (RR 0.80, CI 0.67–0.94, p=0.009), and combined microvascular outcome (RR 0.88, CI 0.79–0.97, p=0.01). Nephropathy alone was not significantly related to intensive control. Severe hypoglycaemia (defined as requiring external help for reversal) was strongly related to intensive control (RR 2.39, CI 1.71–3.34, p<0.001). The researchers also used a statistical technique known as 'trial sequential analysis', which also failed to show mortality benefit with intensive control. This analysis also did not definitely confirm microvascular benefit, but did support the hypoglycaemic risks of intensified blood glucose intervention.

Overall, this important meta-analysis has not supported mortality benefits from tight blood glucose control. Microvascular outcome may possibly be improved, but there is a definite increase in severe hypoglycaemic risk.

These results suggest that some recent suggested very strict target HbA_{1c} levels in type 2 diabetes (e.g. below 6.0%, or below 6.5%) do not seem appropriate in terms of likely benefits and hypoglycaemic risks. A more standard target of 7.0% seems more sensible, and possibly 7.5% may be reasonable. More trials are needed with target HbA_{1c} levels in this sort of range.

Tight glycaemic control is difficult and expensive to achieve, needing wide availability of drugs and insulin, good specialist nurse and dietician support, and self-blood glucose monitoring. African doctors, who rarely have such facilities available, can be reassured by the current trial, as such intensity of control has doubtful benefits. Good lifestyle advice (diet, exercise, smoking etc.) should be delivered, reasonable glycaemic control achieved if possible, and strong attention paid to blood pressure (BP). The UKPDS trial showed strong benefit of BP reduction in type 2 diabetes, regardless of the drugs used,[2] and this is achievable in an African situation, even with limited resources. Lipid control is expensive (in terms of biochemical tests and drugs), but the relevance in African type 2 patients is to some extent uncertain. Optimal BP control (below 130/80 mmHg if possible)[3] may be the most important 'take home' message for African doctors involved with type 2 diabetes treatment.

'Nice' words on hypertension

Following on from the importance of hypertension treatment in type 2 diabetes, new UK recommendations have recently been published on hypertension treatment.[6] These have come from 'NICE' (National Institute for Clinical Excellence), an independent advisory body on cost-effective treatment. The 2011 NICE report contains much that is irrelevant to hypertension care in Africa, including advice on drugs likely to be unavailable or too expensive, and also (controversially even in the UK) the use of ambulatory BP monitoring to make a firm diagnosis.

Nevertheless, and of global importance, the report does emphasise the importance of accurate diagnosis and effective 'to target' treatment. It also emphasises the ethnic differences that exist in responsiveness to anti-hypertensive drug treatments. Beta-blockers and ACE (angiotensin-converting enzyme) inhibitors are less effective in black, compared with white, hypertensive subjects. Beta blockers are now not advised as primary treatment for hypertension, but ACE inhibitors are, of course, widely used. For black patients, NICE advises either calcium channel blockers or thiazide diuretics as first-line treatment. Obviously, drug availability is a major issue in most parts of Africa, but nevertheless, these general principles are worth noting for African doctors involved with hypertension treatment.

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