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

Epidemiology of HIV/AIDS and the scale-up of antiretroviral therapy

The epidemiology of the HIV/AIDS epidemic and the scale-up of antiretroviral therapy (ART) in 2015 was provided by the joint United Nations Programme on HIV/AIDS (UNAIDS).[1] By December 2015, there were an estimated 36.7 (34.0–39.8) million people living with HIV/AIDS globally. Adults constituted 34.9 (32.4–37.9) million and children under the age of 15 years constituted 1.8 (1.5–2.0) million of the global total.[1] In 2015, 2.1 (1.8–2.4) million people were newly infected with HIV and 1.1 (0.94–1.3) million people died from HIV/AIDS. Compared with the previous year, HIV incidence was slightly higher and HIV mortality slightly lower.

Sub-Saharan Africa (divided now in UNAIDS reports into Eastern/Southern Africa and Western/Central Africa) continues to bear the brunt of this epidemic with 25.5 million adults and children (69% of global total) living with HIV in 2015.[1] There were 1.4 million new HIV infections (65% of global total) and 800 000 deaths (73% of global total).[1] Of children living globally with HIV under the age of 15 years, an estimated 1.5 million (83%) resided in sub-Saharan Africa, with 81% of new HIV infections and 82% of deaths in children occurring in this region. Southern Africa remains the worst affected region on the continent, with South Africa continuing to have the largest HIV/AIDS epidemic in the world.

By the end of 2015, there were 17 million people globally receiving ART, representing 46% of people living with HIV.[2] This number was two million more than the 15 million target set by the United Nations General Assembly. In sub-Saharan Africa there has been excellent progress, with over 12 million people on ART by 2015.

In the world's most affected region, Eastern and Southern Africa, the number on treatment has more than doubled since 2010, reaching nearly 10.3 million, representing 54% of people living with HIV. South Africa alone has almost 3.4 million people on treatment, more than any other country in the world. After South Africa, Kenya has the largest ART programme in sub-Saharan Africa with nearly 900 000 people on therapy by 2015. South Africa, Swaziland, Botswana, Zimbabwe, Zambia, Malawi, Mozambique, Kenya, Uganda, Tanzania, Rwanda, and Eritrea all increased treatment coverage by more than 25% between 2010 and 2015.[2]

There has been an alarming slowdown in recent years in the global decline in new HIV infections among adults. In this regard Africa has not done too badly with the largest reduction in HIV incidence being seen in Eastern and Southern Africa where there were about 40 000 fewer new adult infections in 2015 compared with 2010.[2] However, there is no room for complacency. Adolescent girls and young women in Africa are still at particularly high risk of HIV infection due to poor access to education/sexual and reproductive health services, poverty, food insecurity, and violence.

The World Health Organization 2016 Consolidated Antiretroviral Therapy Guidelines

The updated consolidated World Health Organization (WHO) guidelines launched in July 2016 have two key recommendations with respect to treatment: i) ART should be offered to any person living with HIV regardless of WHO clinical stage or CD4 cell count and this includes adults, pregnant and breastfeeding women, adolescents and children; and ii) oral pre-exposure prophylaxis (PrEP) containing tenofovir should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches.[3]

Other new recommendations include: giving dual prophylaxis with zidovudine and nevirapine for the first six weeks of life to high-risk infants born to mothers with HIV; performing routine viral load monitoring at six months, at 12 months and then every 12 months thereafter if the patient is stable on ART; in settings where routine viral load monitoring is available, stopping the monitoring of CD4 cell counts in persons who are stable on ART; using dried blood specimens from venous or capillary blood to determine the viral load with a threshold of 1000 copies/mL to determine virological failure; assessing and managing cardiovascular risk and depression in persons living with HIV as part of the package of HIV care; less frequent clinic visits and medication pick-up (three to six months) for people stable on ART; and distribution of ART to adults, adolescents and children by trained and supervised lay providers.

With 'HIV test and treat' now being official international policy and with attention increasingly being paid to achieving the UNAIDS 90-90-90 targets (90% of individuals with HIV are diagnosed, 90% of those are initiated on ART and 90% of those are virally suppressed), some experts are arguing that the time has come for a more nuanced HIV/AIDS programme design.[4] With this approach, there would be a model of differentiated care in which different types of patient receive different packages of care. HIV services might be different for stable versus unstable patients, for newly diagnosed patients versus those with long standing disease, for adherent versus non-adherent patients and so on. For example, stable patients doing well on ART could be offered longer appointment spacing, fast-track medication refills, community-based drug distribution and inclusion in patient-led community ART groups in an attempt to decongest ART clinics and move treatment closer to communities. In this regard, WHO has published a useful consensus paper defining stable patients (on ART for at least one year, with no adverse drug reactions, no concurrent illness, a good understanding of long-term drug adherence and evidence of treatment success) who need less intensive care and

patients with advanced disease (having a CD4 cell count < 200 cells/uL or being diagnosed with a WHO Stage 3 or 4 defining illness) who need more directed care.[5]

Preventing HIV transmission through antiretroviral therapy

In 2011, a seminal publication based on interim analysis of data from the HIV Prevention Trials Network (HPTN) 052 trial showed that early ART reduced HIV transmission,[6] thus paving the way for early treatment initiation as a public health good. Based on more than five years of follow-up, the definitive findings from this trial published in 2016 were that early ART was associated with 93% lowered risk of linked partner infection compared with delayed ART.[7] Of equal importance was the observation that no linked infections occurred when HIV infection was suppressed in a stable fashion in the index patient.

Early sustained ART is thus crucial to prevent HIV transmission from an infected to a non-infected partner. Pre-exposure prophylaxis (PrEP) provides additional protection to those non-infected partners whose behaviour puts them at high risk of HIV infection. One randomised controlled trial in men who have unprotected anal sex with men showed that on demand treatment with tenofovir and emtricitabine taken before and after sexual activity reduced the risk of HIV infection by 86%.[8] A further open-label pragmatic randomised trial again in men who have unprotected anal sex with men showed that daily treatment with tenofovir and emtricitabine reduced the risk of HIV infection by 86%, refuting concerns that effectiveness of PrEP as determined by randomised placebo-controlled trials would be less in a real-world setting.[9] The findings from these two recent studies provide additional strong support that PrEP should be a standard of care for preventing HIV infection in men who have sex with men and supports increased use of PrEP as an important HIV prevention tool.

HIV-associated tuberculosis

The 2016 Global Tuberculosis Report estimates that of the 10.4 million new cases of tuberculosis (TB) in 2015, 1.2 million were in people living with HIV.[9] The proportion of TB cases living with HIV was highest in the WHO Africa region (31%), and exceeded 50% in some countries in Southern Africa. In the African region, 81% of notified TB cases had a documented HIV test result, and the proportion of HIV-positive TB patients on ART was above 90% in Kenya, Malawi, Mozambique, Namibia, and Swaziland.

In recent years there has been a considerable increase in the provision of isoniazid preventive treatment for TB, especially in the WHO African region. In 2015, there were 910 124 people living with HIV globally who were started on preventive therapy, of whom 856 529 (94%) were in Africa.[9] South Africa, accounted for the largest proportion (45%) of the global total in 2015, followed by Malawi, Mozambique and Kenya. One key question is whether in high HIV and tuberculosis exposure areas continuous isoniazid (defined as treatment for at least 36 months) is more effective than six months. A systematic review found that the risk of active TB was 38% lower amongst patients receiving continuous isoniazid and 49% lower amongst those with a positive tuberculin skin test compared with six months treatment.[10] Amongst those with a positive tuberculin skin test, the risk of death was 50% lower. There was no evidence of increased drug resistance when continuous isoniazid was given and inconsistent findings with regards to adverse effects. Amongst people living with HIV in high TB exposure areas it seems that continuous isoniazid for at least 36-months has several beneficial effects, which probably outweigh the risk of adverse effects.

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Paediatrics Review

Effectiveness of 4CMenB vaccine for infants

The highest incidence of meningococcal disease occurs in the meningitis belt of sub-Saharan Africa and is mainly caused by serogroup A, also C, X and recently W-135.[1] A study of conjugate serogroup A vaccine (licensed in India in 2009) in Chad in 2011-12 demonstrated high efficacy which bodes well for control of the disease when routine administration expands in sub-Saharan Africa.[2] Serogroup C and B predominate in the Americas and Y to a lesser extent with a recent increase in W-135.[2] In Europe and the UK (meningococcal C conjugate vaccine was introduced in the UK in 1999), Australia and New Zealand the main cause of meningitis in children and adolescents is now meningococcal

serogroup B. Most meningococcal disease in Asia is caused by serogroup A and C, but no doubt serogroup B will also be responsible for meningitis in some cases as it is in sub-Saharan Africa outside meningococcal epidemic regions. The polysaccaride vaccine comprising serogroups A, C and W-135, though it has poor immunogenicity in infants and minimal effects on nasopharyngeal carriage, is now given in a single booster dose at 13–15 years in the UK.

Development of an effective conjugate vaccine against serogroup B is constrained owing to the polysaccharide capsule which is structurally homologenous to glycoproteins in foetal neural cell adhesion molecules which makes them poorly immunogenic self-antigens.[3] Development of the 4CMenB vaccine (Bexsero, GSK, Rixensart, Belgium) has demonstrated great potential for control of serogroup B disease. 4CMenB represents three recombinant proteins plus the outer membrane vesicles from the bacteria.

4CMenB vaccine was licensed in Europe in 2013 with a recommendation of a three-dose priming schedule. The UK became the first country to introduce 4CMenB into a national infant immunisation programme, which commenced in September 2015 and uses a reduced two-dose primary schedule at two and four months with a booster at 12–13 months.

During an outbreak of serogroup B meningitis (Men B) at a US university in 2013, the opportunity arose to estimate the serological response to 4CMenB vaccine.[4] Four-hundred and ninety-nine (499) participants received two doses of the vaccine 10 weeks apart but only 66.1% (95% CI 61.8–70.3) were seropositive for the outbreak strains and the geometric mean titre was low (7.6). This caused concern for use of 4CMenB in infants who are less likely to produce an effective response than adolescents.

As MenB disease is relatively rare, undertaking sufficiently powered clinical trials to assess vaccine efficacy is not feasible.[5] In 2015–16, a national observation cohort study of the efficacy of 4CMenB vaccine was undertaken in England.[3] The number of cases of MenB diagnosed in vaccine-eligible children between September 2015 and June 2016 were compared with equivalent cohorts in the previous four years and to vaccine-ineligible children. By six months of age the coverage of 4CMenB in infants eligible for routine vaccination was 95.5% for one dose and 88.6% for two doses. Two-dose vaccine effectiveness was 82.9% (95% CI 24.1–95.2) against all MenB cases. Compared with the pre-vaccine period, reduction in the MenB cases in the vaccine-eligible cohort was 50% [37 cases vs. average 74 cases, IRR 0.50 (95% CI 0.36-0.71) p= 0.0001] irrespective of infants' vaccination status or predicted MenB strain coverage. Also a substantial number of infants who contracted MenB had not completed the two-dose 4CMenB vaccine regimen.

The two-dose 4CMenB priming schedule was highly effective in preventing MenB disease in infants. Cases of MenB in vaccine-eligible infants halved in the 10 months of the programme.

Longer follow-up is required to confirm these results, to assess safety and duration of protection including in adolescents and whether further booster doses are required.[5]

The future of polio vaccination in low- and middle-income countries

In most high-income countries polio vaccination is achieved using inactivated polio vaccine (IPV), which comprises all three serotypes and is often in combination with other vaccines, eg. diphtheria, pertussis, tetanus, and Hib. Up until recently, most low- and middle-income countries (LMIC) used the three oral serotypes (1, 2 and 3, tOPV). Now up to 90 countries have introduced at least one dose of IPV into their routine immunisation programme.[6] From April 2016 serotype 2 component of OPV will be removed from all immunisation protocols.[7] The rationale is that although wild type 2 poliovirus has not been associated with paralytic poliomyelitis (PP) for over a decade type 2 vaccine viruses continue to cause sporadic cases. In LMICs, tOPV will be replaced by bivalent 1 and 3 OPV (bOPV) with supplementary IPV.

There is concern that removing serotype 2 OPV from the schedule may result in reduction of intestinal immunity to serotype 2, which helps to protect person-to-person transmission in countries with poor sanitation and hygiene. This was examined in a large study in four sites, Columbia, Dominican Republic, Guatemala, and Panama, and comprised 940 infants.[8] bOPV provided humeral protection similar to tOPV against serotypes 1 and 3. After one to two IPV doses, in addition to bOPV, 80% and 100% of infants seroconverted, respectively, and the vaccination induced a degree of intestinal immunity against type 2 poliovirus, despite absence of OPV type 2 in the schedule.

Despite the reassurance that the above regimen resulted in some intestinal immunity to serotype 2, the concern is if polio vaccination is inadequate in some LMICs, then children may be vulnerable to outbreaks of poliomyelitis due to type 2. In that situation it will be necessary to rapidly implement an emergency course of monoOPV 2 vaccination in the area.[7]

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