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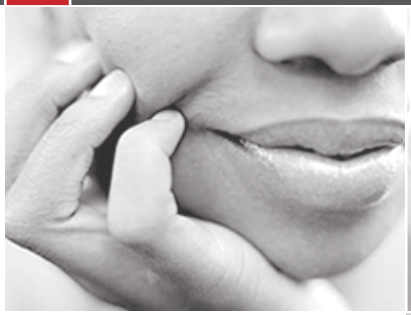

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SINGLE DRUG SWITCH FROM STAVUDINE (OR ZIDOVUDINE) TO TENOFOVIR

Many clinicians consider switching a patient on first-line ART from stavudine (or zidovudine) to tenofovir either because side effects such as lipoatrophy, neuropathy or anaemia have developed or because they wish to avoid the side effect profile associated with stavudine and zidovudine, particularly lipoatrophy.

However, there are two important issues to consider before making such a single drug switch:

1) Before a patient is prescribed tenofovir the **serum creatinine** should be checked and the **estimated creatinine clearance** calculated. Tenofovir is nephrotoxic in a small proportion of patients, but the risk is higher in those with underlying renal impairment. Tenofovir should be avoided in patients with creatinine clearance < 50ml/min.

2) The patient's **HIV viral load** should be checked. The reason is that if a patient has virological failure on first line ART and a single drug switch to tenofovir is made then resistance to tenofovir may rapidly develop (due to the K65R mutation). If the switch to tenofovir is being made within the first 6 months of first line ART it may be assumed that resistance to first line has not yet developed (provided there has been good adherence) and a switch to tenofovir can be made without checking the viral load first. However, if a switch to tenofovir is considered beyond 6 months then the viral load should be checked first. If the viral load is undetectable (VL < 50 copies/ml) then the switch can be safely made. However, if the viral load is detectable (VL > 50 copies/ml) then the switch should be deferred, additional adherence counseling provided and the viral load should be repeated in 3 months. If the viral load is now undetectable then the switch can be safely made. If viral load is still not suppressed at this stage then consideration should be given to switching to second line ART (which may contain tenofovir).

Sometimes the viral load may not be suppressed initially, but the clinician may not want to defer 3 months because the patient has side effects (eg. neuropathy) that may worsen if a switch is deferred. Such cases should be discussed with AfA as the approach needs to be individualized.

LONG TERM ISONIAZID PREVENTIVE THERAPY FOR HIV-INFECTED ADULTS: NEW EVIDENCE

Tuberculosis is the commonest cause of morbidity and mortality in HIV-infected adults in Africa. Preventive therapy, either with isoniazid or with combination therapy, has been shown to reduce the risk of tuberculosis. The most widely studied preventive therapy regimen is isoniazid for 6 months. Meta-analyses show that preventive therapy is only effective in patients who are tuberculin skin test (TST) positive.[1]

One of the limitations of isoniazid preventive therapy (IPT) is the limited duration of benefit. Follow on studies of randomised controlled trials of IPT conducted in Uganda[2] and Zambia[3] found that the duration of benefit was 6 months and 18 months respectively, but neither study was adequately powered to answer the question of duration of benefit. Two recent southern African studies have reported results of long term IPT and both included control arms of isoniazid for 6 months.

A study in Soweto randomised TST positive adults not yet eligible for antiretroviral therapy (ART) to one of 4 arms: isoniazid 6 months, isoniazid continuous, rifampicin plus isoniazid (administered twice weekly) 3 months, and rifapentine plus isoniazid (administered weekly) 3 months. In their intent to treat analysis isoniazid continuous was not superior to 6 months for developing tuberculosis.[4] Continuous isoniazid was associated with a higher risk of adverse events. In a subsequent as-treated analysis (limited to patients who tolerated the treatment and were not lost to follow up) isoniazid continuous was superior to 6 months with a 69% reduction in tuberculosis incidence.[5]

More encouraging results favouring long term IPT were reported from a trial in Botswana, which included many more participants in the long term IPT arm than the Soweto study (1006 and 164 respectively) and had lower rates of loss to follow up. Participants in the Botswana study were enrolled irrespective of TST status and randomised to receive isoniazid for 36 or 6 months.[6] The incidence of tuberculosis was significantly reduced in the isoniazid 36 months arm. As with all other studies, only participants with a positive TST benefitted: tuberculosis incidence was reduced by 92% (P=0.015) and 8% (P=0.69) for TST positive and negative participants respectively. The duration of benefit of isoniazid appeared to be around 6 months after stopping. Approximately half the participants commenced ART after enrolling into the study, which independently reduced the risk of tuberculosis by half. There was a reduction in death in TST positive participants in the 36 months IPT arm of 72%, but this just failed to reach statistical significance. Of concern is that death rates were 3-fold higher in TST negative participants randomised to 36 months IPT, which is unexplained as only one death seemed directly attributed to isoniazid.

IPT is a useful intervention, but is seldom given. AfA recommends TST be done in all patients who do not immediately qualify for ART, and IPT should be given for all who are TST positive. We recommend that 6 months IPT be given, but 36 months IPT should be considered in view of the exciting results from the Botswana study. If ART is commenced before the 36 months IPT is completed then IPT should be continued for the full 36 month period. Retrospective studies suggest that IPT is beneficial in patients on ART, but we do not recommend this until results are available from a randomised controlled trial that is being conducted in South Africa. It is essential to first exclude active tuberculosis before commencing IPT. Studies have shown that symptoms of tuberculosis (cough, night sweats, fever or weight loss) are adequate to rule out tuberculosis – patients without symptoms can commence IPT with no further investigations.

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IMMUNIZATION AND HIV IN ADULTS

General principles that apply to vaccination in adults with HIV-infection are:

1. In general, HIV-infected persons should avoid live vaccines, although Yellow Fever and MMR may be given to patients with CD4 cell counts > 200 cells/uL.
2. Vaccine efficacy is reduced in HIV-infected persons with advanced immunosuppression. Some vaccine courses will require extra or booster doses, depending on the individual vaccine.
3. Duration of vaccine efficacy may be reduced in HIV infection, particularly in those with advanced immunosuppression.
4. A lack of antibody response does not always equate with lack of efficacy.
5. When considering vaccinations for HIV-infected travellers, the need for travel to a high risk area should be balanced with the risk of increased disease severity in HIV-infected travellers, particularly in those with advanced immunosuppression. If travel can be avoided or delayed until immune reconstitution has taken place following instigating highly active antiretroviral therapy, then this should be discussed at every opportunity.

Vaccine	Indication	Notes
Live Vaccines		
Cholera (CVD103-HgR)	Contraindicated	Use inactivated oral vaccine.
Influenza (intranasal)	Contraindicated	Use inactivated parenteral vaccine. Avoid vaccination in household contacts.
Measles, Mumps, Rubella (MMR)	Indicated for measles IgG-seronegative persons with CD4 count > 200 cells/uL. Contraindicated if CD4 ≤ 200 cells/uL.	Avoid pregnancy for 1 month after vaccination. Breast feeding not contraindicated. Administer 2 doses at least 1 month apart to increase likelihood of protection against measles. Safe for household contacts.
Poliomyelitis (oral; OPV)	Contraindicated	Avoid vaccination in household contacts.
Tuberculosis (BCG)	Contraindicated	
Typhoid (Ty21a)	Contraindicated	Use inactivated Typhoid ViCPS vaccine.
Varicella-zoster (Chickenpox)	Varicella seronegative patients with CD4 count > 200 cells/uL.	Pregnancy should be avoided for 1 month after vaccination.
Yellow Fever	Indicated if significant risk of contracting YF for travellers with CD4 count > 200 cells/uL, whether or not on antiretroviral therapy. Contraindicated in HIV-infected travellers: · with CD4 ≤ 200 cells/uL. · who are > 60 years of age. · on CCR5 inhibitors†. · with egg allergy. · pregnant or breast feeding.	Decisions regarding YF vaccination should always be taken in light of likely risk of acquisition of infection. An exemption certificate should be provided to all travellers not vaccinated, but travelling to a YF endemic country. Focused advice on avoidance of mosquito bites must be stressed. Safe for household contacts. Re-vaccinate after 10 years.
Zoster (Shingles)	Contraindicated	VZV titre ≥5 times that of chickenpox vaccine.
Inactivated Vaccines / Toxoids		
Cholera (WC/rBS)	Indicated in travellers to high risk areas during epidemics or after natural disasters.	Limited efficacy and safety data. Responses in travellers with CD4 <100 cells/uL are poor. Stress good food and water hygiene.
Cholera (Dukoral®)	Protects against V.cholerae-O1 subtype.	No efficacy data available specifically in HIV-infected patients.
Diphtheria/Tetanus/Polio (parenteral Td/IPV)	Booster dose every 10 years.	No need to re-start a course, irrespective of the time elapsed since last dose.
Hepatitis A	Should be considered for all HIV-infected individuals without evidence of immunity, but particularly in patients with comorbid liver disease, non-immune travellers to endemic areas and MSM.	If resources allow, check for serological evidence of natural infection before vaccination. Serological responses reduced in immunosupressed patients, but good efficacy even at low CD4 count. Two or three doses required. May be given as single vaccine or as combination with Hepatitis B.

Vaccine	Indication	Notes
Inactivated Vaccines / Toxoids		
Hepatitis B	Recommended for all non-immune HIV-infected adults.	4 dose schedule (0,1,2,12 months) ± booster doses as dictated by serological response. Those who fail to respond to 1st vaccination course should either receive a 2nd course with single or double-dose vaccine. Stress advice on risk reduction, especially in high risk groups such as MSM.
Influenza	Annual vaccination for all HIV-infected patients with CD4 cell count > 100 cells/uL and those on ART whose CD4 count does not rise above 100 cells/ uL.	Patients whose CD4 count < 100 cells/uL, who are ARV-naïve should start ART and be vaccinated once CD4 count rises.
Japanese B encephalitis	Indicated for travellers to south-east Asia and Far East staying > 1month in endemic areas, particularly for those travellers whose work puts them at high risk‡.	Formalin-inactivated JEV vaccine linked with severe neurological adverse events. A new JEV vaccine, Ixiaro, inactivated virus strain derived from tissue culture has recently been licensed by the FDA. No information is available yet for HIV-infected persons.
Neisseria meningitidis	Consider in young adults and patients with functional or anatomic asplenia. Mandatory for visitors to the Hajj. Indicated for travellers to the 'Meningitis belt'.	Single dose quadrivalent (ACWY) vaccine recommended. No evidence of increased risk of adverse events in HIV-infected persons.
Pneumococcus	PPV-23 is indicated for HIV-infected patients with functional or anatomic asplenia or chronic lung disease.	Studies in developed countries suggest a reduction in pneumococcal disease in those with CD4 count > 500 cells/uL, but not below[1]. In Ugandan ARV-naïve adults, increased number of pneumonias were seen in vaccinated, but paradoxically, 16% reduction mortality was reported in those that were vaccinated[2].
Rabies	Indicated for all travellers to dog-rabies endemic areas.	Intramuscular immunization recommended rather than intradermal. Asses response to immunization in travellers with CD4 ≤ 200 cells/uL, if resources allow ± further boosting if antibody response > 0.5IU.mL not achieved. Counsel all travellers to endemic areas on wound treatment and post-exposure prophylaxis.
Tick-borne Encephalitis	Indicated for HIV-infected travellers intending to walk, camp or work in heavily forested regions in endemic areas.	Limited efficacy data available. Highest risk in late spring/early summer. Travellers with CD4 count >400 cells/uL had better serological response. Stress avoid tick bites and consumption of unpasteurized milk.
Typhoid (ViCPS)	Indicated for HIV-infected travellers at risk of exposure, particularly to highly endemic areas.	Booster every 3 years. Serological response reduced in travellers with CD4 count ≤ 200 cells/uL. Stress importance of food and water hygiene.

† A severe viscerotropic disease after YF vaccination described in an HIV-negative person with genetically determined disruption of the CCR5- RANTES axis.

‡ Participants in extensive outdoor activities in rural areas

1 Dworkin et al. Clin Infect. Dis 2001;32: 794-800

2 Watera et al. AIDS 2004; 18: 1210-13

There are 5 important points for consideration regarding immunization in HIV-infected children. These are the immunogenicity of standard vaccines, the dangers of dissemination of live attenuated organisms, the risk of increased viral replication due to immunization, the role of new vaccines and the impact of HAART. There are new data on all aspects, although there are still many gaps in our knowledge. There is also a lack of awareness on the increased susceptibility of South African HIV-infected children to many vaccine-preventable diseases, despite previous immunization.

Poor immunogenicity

Poor immunogenicity to Measles, Mumps and Rubella (MMR) vaccine is well described in HIV-infected children, with good antibody response after re-immunization after immune reconstitution in response to HAART (CD4 <15% rising to >15% for >3 months).[1] At baseline, only 42% of previously immunized children were protected against measles. Similar data from Zambia shows poorer response to immunization and more rapid decline in antibody levels than in HIV-uninfected infants.[2]

In a cohort from USA, also on HAART, only 24% of previously immunized children and adolescents were protected against Hepatitis B virus (HBV), with only 45% developing an adequate antibody response to re-immunization.[3] In a subsequent study, where the dose of HBV was increased from 5 to 10ug per dose, the response was improved to 80% achieving protective antibody levels.[4]

Danger of dissemination of live attenuated organisms through immunization

Bacille Calmette-Guérin (BCG) immunization is usually given in the first week of life and is contra-indicated in HIV-infected infants. Disseminated BCG has mortality in excess of 75%, but was described in a setting of poor access both to early diagnosis and access to ART. In areas endemic for both HIV and TB, BCG should still be given.[5] Immune reconstitution inflammatory syndrome (IRIS) in response to BCG, although the most common cause of IRIS in children is far less of a problem with early ART.[6]

Live Oral Polio Vaccine (OPV) has been given to HIV-infected infants for almost 20 years in South Africa, with no reported cases of vaccine-related polio, apart from a single case in Zimbabwe in 1999.[7] Vaccine-derived polio has been linked to paralysis after spread in the household.[8] In the South African Expanded Program for Immunization (EPI), the first dose of OPV is given at birth, with inactivated polio vaccine at 6, 10 and 14 weeks, partially minimizing the risk of spread in households.

The Global Advisory Committee on vaccine safety recently reviewed the safety data of measles vaccine and concluded that it was safe for HIV-infected children, but expressed caution due to lack of data.[9]

Impact of immunization on HIV replication

Immunizations cause a transient increase in viral load[10], which is probably not clinically significant. Increases in viral load after immunization are not seen in children on antiretroviral therapy[11].

New and older vaccines

Pneumococcal disease causes much morbidity and mortality in HIV-infected children. The conjugated pneumococcal vaccine (PCV) is effective in HIV-infected children[12] and has just been introduced in to the South African EPI. It is important that all HIV-infected (and other immunocompromised children) who have not previously been immunized, receive 2 doses of PCV at least one month apart for “catch-up” as they are vulnerable to invasive pneumococcal disease despite HAART. Rotavirus vaccine containing attenuated live virus, is also part of our EPI and in a pivotal study, was safe in HIV-infected infants.[13]

Human Papilloma Virus (HPV) is an important carcinogen not only affecting the cervix, but also the oropharynx and anogenital area. While less immunogenic in HIV-seropositive adolescents, it should be given to both males and females. The vaccine does not contain live virus so can be given without fear of introducing infection.[14]

Varicella Zoster Virus (VZV) can cause severe disease, especially in immunocompromised children. VZV vaccine can safely be given to HIV-infected children above 12 months of age with mild disease and CD4 >15%. A second dose should be given 3 months later.[15]

Influenza causes severe morbidity in HIV-infected children. Trivalent inactivated vaccine should be given to all children. A recent meta-analysis suggest moderate efficacy only.[16] Currently, increasing the dose of immunogen is being evaluated.

Impact of HAART in response to immunization

A key factor in immunization is early access to ART. In a recent study, Madhi established for the first time that early HAART started in infants below 12 weeks of age produced a better quality of antibody to PCV than a deferred strategy, despite similar quantitative responses.[17]

The future

Many HIV-infected children are vulnerable to vaccine-preventable infections despite previous immunization. Children immunized before access to HAART or without full immune recovery on HAART should be re-immunized.[18]

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