Evidence-based treatments for the asymptomatic HIV-positive patient in general practice

Increasing numbers of HIV-positive, but healthy, people make a rational approach to their treatment vital.

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The South African Department of Health estimates the national HIV seroprevalence to be 24.8%.[1] The highest is found in KwaZulu-Natal (KZN) at 33.5% and the lowest in the Western Cape (WC), with a seroprevalence of 8.6%. Although these figures were obtained from women aged between 15 and 49 years attending public antenatal clinics, they may be extrapolated to the sexually active population as a whole. Further, the overwhelming majority of the women attending antenatal clinics are healthy and therefore asymptomatic. From this research and others[2] one can conclude that the number of asymptomatic HIV-positive patients seen in a typical general practice today is significant and covers all age groups and races. The challenge is to manage them using the best available evidence. This is compounded by the fact that South African doctors practise in a resource-constrained environment, and most doctors in general practice today were trained when HIV was either not present or not as common as it is today.

The challenges are divided into two sections which are likely to represent patient population profiles seen in general practice:

- the adult non-pregnant HIV-positive asymptomatic patient
- the HIV-positive pregnant asymptomatic patient.

The following simple grading system is used for judging and recommending what is and what is not good research evidence of the effect of an intervention:

- A grade: treatment evidence based on a systematic review (SR) of randomised controlled trials (RCTs) and/or from a well-designed large RCT
- B grade: treatment evidence based on a RCT that is not well designed, with inadequate power to answer the research question or methodologically flawed
- C grade: treatment evidence based on observational studies (non-RCT or SR)
- D grade: treatment evidence based on personal experience and recommendations.

THE ASYMPTOMATIC HIV-POSITIVE ADULT NON-PREGNANT PATIENT IN GENERAL PRACTICE

To test or not to test

The first practical problem is getting a patient suspected from clinical history and examination to be HIV-positive, to agree to testing. There is no research that looks at interventions at the general practice level that would lead to an increase in the number of patients volunteering for testing. However trust between the patient and the doctor, assuring confidentiality and the patient seeing value in knowing his/her HIV status, seems to be important. Knowing HIV status should translate into a decrease in the patient's risk of falling ill from opportunistic infections and malignancies and eventually from premature death. The risk of opportunistic infections

increases significantly when the CD4 count falls below 250/mm^3.[3]

Preventing opportunistic infections in the asymptomatic HIV-positive patient

Is antituberculosis prophylaxis beneficial?

There is grade-A evidence from two SRs[4,5] and several well-conducted RCTs[6-9] that shows that in people who are both HIV- and tuberculin-positive, prophylactic anti-TB drugs significantly reduce the risk of active TB in the short term.There is evidence that without anti-TB prophylaxis, patients who are HIV- and tuberculin-positive have a 50% or more lifetime risk of developing TB compared with a 10% risk in those who are tuberculin-negative.[10] Anti-TB prophylaxis in this context becomes of tremendous value to the asymptomatic HIV patient in general practice.The magnitude of the benefit for patients randomised to isoniazid prophylactically (or in combination with pyrazinamide) versus patients randomised to receive placebo was a 76% decrease in TB over 2 - 3 years (RR compared with placebo 0.24, 95% CI 0.14 - 0.40) in the SR by Bucher *et al.*[5] There was also a trend towards a reduction in deaths (RR compared with placebo 0.77, 95% CI 0.58 - 1.03). One assumes that if the studies had a longer follow-up period the difference in death rates would have been significant. Giving anti-TB prophylaxis in tuberculin-negative patients has been shown to be no different from no treatment or placebo.

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Which anti-TB prophylactic regimen?

There is grade-A evidence from the well-conducted RCT referenced above, that there is no difference in the rate of TB recurrence or infections, between using pyrazinamide with rifampicin in combination versus isoniazid alone, in HIV-positive and tuberculin skin-positive patients.

For how long should a patient take anti-TB prophylaxis?

The RCT evidence above compared 2 - 3 months' treatment per year for combination treatment (rifampicin and pyrazinamide) versus 6 - 12 months' treatment with isoniazid.

In summary

- There is grade-A evidence that HIV-positive patients who are tuberculin skin-positive benefit from anti-TB prophylaxis. (Advice: HIV-positive patients should have a tuberculin skin test and should be offered prophylaxis if found to be positive.)
- There is no difference between the short-term (2 - 3 months) combination therapy and the long-term (6 - 12 months) isoniazid therapy. These regimens should be followed yearly if on short course. (Advice: individualise in consultation with the patient regarding side-effects, cost and compliance.)

Is prophylaxis against Pneumocystis carinii *pneumonia (PCP) and toxoplasmosis beneficial?*

There is grade-A evidence from SRs[11] and RCTs[12,13] that trimethoprim/sulfamethoxazole (TMP-SMX) — co-trimoxazole — is more effective than pentamidine or placebo at reducing the risk of PCP or toxoplasmosis infections in patients who are HIV-positive. Patients given TMP-SMX (Bactrim equivalent) had a 68% decrease in the risk of PCP compared with those given placebo (RR 0.32, 95% CI 0.23 - 0.46) and a 42% greater risk reduction compared with those given aerolised pentamidine (RR 0.58, 95% CI 0.45 - 0.75).

Which dose of TMP-SMX?

There was no significant difference in the rate of PCP infections between patients on high doses (160/800 mg daily) and those on low doses (160/800 mg 3 times weekly or 80/400 mg daily).

In summary

- There is grade-A evidence that prophylaxis with TMP-SMX in low doses is beneficial in decreasing PCP and toxoplasmosis infections.
- Higher doses of TMP-SMX are associated with an increase in severe side-effects (rash, fever) which may lead to poor compliance.

Does prophylaxis with antifungal drugs decrease the incidence of candidiasis in the asymptomatic HIV-positive patient?

Grade-A evidence from a RCT[14] found that women taking weekly fluconazole had a 58% decrease in the incidence of candidiasis compared with a 44% decrease in those

taking placebo (RR 0.56, 95% CI 0.41 - 0.77). Fluconazole was found to be more effective than clotrimazole in decreasing the incidence of invasive fungal disease and mucocutaneous candidal infections (11% decrease v. 4%).[15]

Which dose of fluconazole?

There was no difference in the rate of invasive fungal infections between high-dose fluconazole (200 mg daily) and low doses (400 mg once a week).[16]

In summary

- There is grade-A evidence that fluconazole given prophylactically once a week (400 mg) significantly decreases the incidence of candidal mucocutaneous infections.

Does prophylaxis with aciclovir, valaciclovir and famciclovir decrease the risk of cytomegalovirus (CMV), herpes simplex virus (HSV) and varicella zoster virus (VZV)?

There is grade-A evidence from a SR[17] that in patients who were both asymptomatic and had full-blown AIDS, there was no difference in the incidence of CMV between those randomised to aciclovir compared with those who received no treatment or placebo. However there was a significant decrease in HSV and VZV ($p < 0.001$). One RCT[18] in patients with CD4 counts < 100 showed an increased mortality in the valaciclovir group ($p = 0.06$), but a lower rate of CMV infection compared with those allocated to aciclovir (12% v. 18%; $p = 0.03$). Another RCT found that patients with frequent recurrences of HSV who took famciclovir had decreased HSV infections (HSV isolated in 9/1 071 famciclovir days v. 122/1 114 placebo days; $p < 0.001$).[19]

In summary

- There is evidence from a SR that shows that aciclovir does not reduce the incidence of CMV compared with placebo, but significantly decreases HSV and VZV and overall mortality.
- There is evidence from a RCT that prophylaxis with valaciclovir reduces the incidence of CMV when compared with aciclovir but is associated with an increase in mortality in severely compromised patients. (NB: Use valaciclovir with caution in patients with CD4 counts < 250 mm^3.)

Is there evidence for prophylaxis against* Mycobacterium avium *complex (MAC) in the asymptomatic HIV-positive patient?

There are no SRs or well-conducted RCTs (grade-A evidence) that address the question of azithromycin and clarithromycin, either alone or in combination, in asymptomatic HIV-positive patients. Two trials have been done in patients with AIDS as the risk of developing MAC increases with lower CD4 (< 50 mm^3) counts.[20]

THE PREGNANT ASYMPTOMATIC HIV-POSITIVE PATIENT IN GENERAL PRACTICE

The following questions need to be addressed:

- What is the evidence regarding the use of antiretrovirals (ARVs) in preventing mother-to-child transmission (MTCT)?
- Which regimen of ARVs should be used and what about vitamin A and multivitamin supplements, taking into consideration the efficacy data and the fact that South African doctors practise in a resource-poor environment?
- How should the patient be delivered?
- Should the patient breast-feed after delivery?

What is the evidence regarding the use of ARVs in preventing MTCT?

There is grade-A evidence from a SR[21] which compared zidovudine given antenatally, during labour and after labour (for 6 weeks to the baby and mother and with no breast-feeding in the Connor *et al.*[22] trial), which found that zidovudine decreased the incidence of HIV in infants by 46% (RR 0.54, 95% CI 0.42 - 0.69). The absolute risk reduction (ARR) was 11% which translates to a number needed to treat (NNT) of 9 (95% CI 7 - 14). In other words, using this regimen one needs to treat on average only 9 HIV-positive pregnant mothers to prevent 1 infant from getting AIDS. Even when shorter regimens were used several RCTs[22-24] showed that the NNT is still low at 11.

Which regimen of ARVs should be used?

When short-course (mother treated from 35 weeks of pregnancy and during labour and the infant given treatment with zidovudine for up to 3 days) zidovudine regimens were compared with no treatment or placebo, there was on average a 40% decrease in the incidence of infant AIDS, with a NNT of 11.[23,24]

There is grade-A evidence from RCTs[27,28] which show that vitamin supplements are no different from no treatment or placebo for the infant HIV incidence.

Should you use nevirapine or zidovudine?

There is grade-B evidence from an unblinded RCT[21] that compared intrapartum and neonatal single-dose nevirapine (one dose to mother during labour and single

dose to baby within 72 hours of birth) with zidovudine (given orally during labour and for 7 days to the baby) for prevention of MTCT of HIV-1 in Kampala. Single-dose nevirapine was found to decrease the incidence of HIV in the infants at 14 - 16 weeks by 42% (RR 0.58, 95% CI 0.40 - 0.83) when compared with those given zidovudine.

How should the patient be delivered?

There is grade-A evidence from a SR[21] that shows that elective caesarean section (CS) at 38 weeks decreases the number of infants with HIV at 18 months by 84% (RR 0.16, 95% CI 0.05 - 0.55; NNT = 11) when compared with spontaneous vaginal delivery. However in our setting, where operating theatre time and other resources are limited and where sepsis may be important, this method of delivery should be individualised to patients who have access to full surgical delivery options.

Should the patient breast-feed after delivery?

There is grade-A evidence from a RCT[29] that compared the effect of breast-feeding and formula feeding on transmission of HIV-1 and found that in mothers who breast-feed their babies, there was a 100% increase in the number of infants with HIV at 24 months (RR 2.0, 95% CI 1.4 - 3.0). In other words, for every 6 mothers who do not breast-feed (and are provided with clean water and formula feeds) 1 infant will avoid getting infected with HIV. Again the implementation of this intervention must be individualised and applied to patients who have access to clean water, formula feeds and health education. If they do, this is a very effective intervention.

In summary

- ARVs (zidovudine and nevirapine) significantly decrease MTCT of HIV.
- In our resource-poor environment, the single-dose nevirapine regimen for mother and baby is preferable to short courses of zidovudine.
- For those patients who have access to ARV, the earlier the zidovudine is used (from 28 weeks of pregnancy and for 6 weeks in the infant), the lower the risk of MTCT.
- Bottle feeding is a very effective way of preventing MTCT as long as the mother has access to clean water, formula feed with heating facilities and health education and care.
- Elective caesarean section is an effective way of preventing MTCT in a population that has access to surgical resources,ARVs before and after delivery, formula feeds, education and health support.
- Vitamin A or vitamin supplements are no better than placebo or no treatment as an intervention for preventing MTCT.

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IN A NUTSHELL

The asymtomatic HIV-positive patient represents a significant percentage of patients seen in general practice today in South Africa.

It is important and beneficial to know a patient's HIV status in order to prevent HIV-related morbidity and mortality.

Anti-TB drugs given prophylactically to HIV-positive and tuberculin skin-positive patients reduce their risk of active TB by as much as 70% in the short term (2 - 3 years).

Trimethoprim/sulfamethoxazole (TMP-SMX) — co-trimoxazole — is more effective than pentamidine or placebo and can reduce the risk of PCP or toxoplasmosis in patients who are HIV-positive by as much as 60%.

Women taking weekly fluconazole have a 58% decrease in the incidence of candidiasis compared with a 44% decrease in those taking placebo.