HIV POST-EXPOSURE PROPHYLAXIS AND ANTIRETROVIRAL THERAPY FOR ADULTS AND ADOLESCENTS: A PRACTICAL GUIDE FOR SURGEONS AND GENERAL PRACTITIONERS

As HIV has become a chronic manageable condition, with patients living longer, so the risk of transmission to health care workers has potentially increased.

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The introduction of triple antiretroviral therapy has resulted in substantial reductions in progression to AIDS, opportunistic infections, hospitalisations, and deaths.[1] HIV has become a chronic, manageable condition with HIV-infected patients living longer and consequently undergoing more surgical procedures. The current belief is that the risks of surgical complications for HIV patients can be predicted in a way similar to the method used in HIV-negative patients. Some studies, however, did show that the lower the CD4 count or the higher the viral load (>30 000 HIV RNA copies per ml of blood) the higher the risk of secondary infections or complications.[2]

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HIV post-exposure prophylaxis (PEP) for needle-stick or sharps injuries

Prospective surveys show the risk of HIV seroconversion after a single hollow-bore needle-stick injury involving known HIV-infected blood to be approximately 0.36%.[3,4] The risk after a solid needle-stick injury or after mucocutaneous exposure is much lower, probably in the region of 1/1 000. Drugs must be commenced within 1 - 2 hours (preferably not later than 8 hours) but are probably still indicated 3 days after exposure – better late than never. All drugs should be taken for 28 days and it should be noted that nevirapine (Nev) or abacavir (ABC) should never be used for PEP due to the risk of liver toxicity (Nev) or hypersensitivity reaction (Nev/ABC). If the source patient has previously used antiretroviral therapy or is currently on treatment it is best to ask for an expert opinion. This is especially important if the source person's viral load (VL) is above detection limits or if a recent undetectable VL is not available, since it might imply potential resistance to the standard PEP regimens.

Summary of the recommended PEP regimens – the SA HIV Clinicians Society[5] (advise the use of 3 drugs in the South African context:

- Regimen
  1. D4T 30 mg 2x/day (fewer side-effects compared with AZT on short-term use)
  2. 3TC 150 mg 2x /day
- Alternative regimen
  1. AZT 300 mg 2x/day
  2. 3TC 150 mg 2x/day
     Combivir = AZT + 3TC 1 tab 2x/day
- Alternative regimen
  1. Truvada = Tenofovir + FTC (300 mg/200 mg) 1 tablet per day (FTC 200 mg once daily is not available in SA) *or*
  1. Tenofovir 300 mg 1x/day *plus*
  2. 3TC 150 mg 2x/day or 300 mg 1x/day

Third drug

  3. Lopinavir/ritonavir (Aluvia) 2 tabs 2x/day *or*
  3. Efavirenz 600 mg nocte

The majority of international guidelines (e.g. CDC guidelines) recommend the use of a third drug only in case of a high-risk injury, which includes:

- very deep penetration
- visible blood on needle
- exposure from a patient with a high viral load (acute seroconversion or end-stage HIV illness)
- if antiretroviral therapy was started >8 hours after exposure.

Antiretroviral therapy

Goals of therapy

- Durable suppression of HIV viral load to less than 50 copies/ml.
- Improvement in quality of life.
- Preservation of future therapeutic options – poor compliance is a known risk factor for the selection of HIV viral mutations with possible cross-resistance to other antiretroviral agents.
- Restoration of immune function (as indicated by the CD4 cell count).
- Prevention of HIV transmission.

When to start antiretroviral therapy (Table I)

Patient readiness for therapy is critically important before commencing therapy since commitment to lifelong treatment with at least 95% adherence is needed for long-term success. New data and considerations support initiating therapy for asymptomatic patients before CD4 cell count declines to less than 350 cells/μl[3,6] In patients with CD4 cells/μl of 350 or more the decision to begin therapy should be individualised and based on the presence of co-morbidities, risk factors for progression to AIDS and non-AIDS diseases and patient readiness for treatment. In addition, a high plasma viral load (>100 000 copies/ml) and rapidly declining CD4 cell count (>100/μl^3 per year) should prompt treatment initiation. Active hepatitis B or C virus co-infection, cardiovascular disease risk and HIV-associated nephropathy also prompt earlier therapy.

The South African antiretroviral treatment guidelines for 2010[7] are an attempt to bring South Africa in line with international best practice.[6,8,9] Treatment will be started for pregnant HIV-positive women with a CD4 count of 350 or with symptoms regardless of their CD4 count. Pregnant women with CD4 counts above 350 will receive PMTC treatment from 14 weeks of pregnancy to protect the baby. Persons with HIV/TB co-infection will be started on antiretroviral therapy at CD4 counts of 350 or less. WHO stage 4 disease as well as MDRTB or XDRTB patients are also considered eligible to start antiretroviral therapy irrespective of

their CD4 count. Some other proposals are the expanded use of fixed dose combinations and enabling nurses and primary health care facilities to initiate antiretrovirals. We need to continue the campaign for the provision of antiretrovirals to all HIV-positive people with a CD4 closer to 350.[9] The new SA guidelines are welcome news and hopefully it will improve the current situation in South Africa where patients on average start antiretroviral therapy with very low CD4 counts (in the Free State the average is about 70 cells/µl).

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Concomitant antiretroviral therapy during TB therapy is complicated by high pill burden, overlapping drug toxicities, concerns about drug-drug interactions and paradoxical immune reconstitution reactions. Latest research shows a benefit to patients if antiretroviral therapy is initiated sooner after commencing with TB treatment rather than delaying ARV treatment. For patients who tolerate their TB treatment, it is usually safe to start antiretroviral therapy after about 2 weeks on TB treatment.

ARV combinations to start in antiretroviral-naïve patients

Drug selection is becoming increasingly complex, with about 27 antiretroviral medications available in five major classes. The first regimen offers the best chance of success and once treatment failure occurs it becomes more difficult to achieve full viral suppression. After failure of second-line therapy limited options are available, especially in resource-poor settings like South Africa. ARV regimens are composed of a 'base' and a 'backbone'. The base is mostly either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI), with the 'backbone' typically consisting of two nucleoside reverse transcriptase inhibitors (NRTIs). Four-drug regimens are no more effective than three-drug regimens and may be associated with greater toxicity. The ultimate choice of regimen should be based upon individual patient considerations, such as ability to adhere, concurrent medications, regimen complexity, tolerance, pregnancy potential, and medical co-morbidities.[1]

The South African 2010 guidelines[7] undertake to phase out stavudine/d4T (the drug with by far the most side-effects[9]). The proposal is to replace it with tenofovir (TDF) as first-line therapy for all new patients needing treatment, including pregnant mothers. Patients currently on a d4T-based regimen will remain on d4T if they have no side-effects, but the guidelines will enable patients with any toxicity to switch to tenofovir early as well as substituting TDF if patients are at high risk for d4T or AZT toxicity (high BMI, low Hb, older females, etc.). Efavirenz is the preferred drug to use for TB/HIV co-infected patients as 'base' because nevirapine increases the risk of liver toxicity and lopinavir/ritonavir combination increases the risk of drug-drug interactions (remember to double the dose of lopinovir/ritonovir if used with rifampicin).

The 2008 IAS-USA guidelines[8] for initial antiretroviral therapy recommend either of two basic three-drug regimens: efavirenz plus two NRTIs, *or* a ritonavir-boosted protease inhibitor (lopinavir, atazanavir,

Table I. Summary – Initiation of antiretroviral therapy in antiretroviral-naïve patients

Clinical category	CD4 cells/µl	HIV RNA copies/ml	Recommendations*
Symptomatic or AIDS-defining illness	Any	Any	Start antiretroviral therapy ** DHHS guidelines AI
WHO stage 4 disease	Any	Any	2010 SA guidelines
Pregnancy	Any <350 (or stage 3 or 4 disease)	Any Any	** DHHS guidelines AI 2010 SA guidelines
HIV-associated nephropathy	Any	Any	** DHHS guidelines AII
Hepatitis B virus (HBV) co-infection when treatment of HBV is indicated	Any	Any	** DHHS guidelines AIII
TB	CD 4 <350	Any	2010 SA guidelines
MDRTB or XDRTB (Multi- or extensively drug-resistant tuberculosis)	Any	Any	2010 SA guidelines
Asymptomatic	<200	Any	Start antiretroviral therapy
Asymptomatic	<350	Any	Start antiretroviral therapy (majority of experts – WHO etc.) ** DHHS guidelines AI
Asymptomatic	>350 Or rapidly declining CD4 (>100 cells/µl/year)	>30 000 (bDNA) or >50 000 (RT-RNA)	Start antiretroviral therapy especially if >100 000 copies/ml (majority of experts)
Asymptomatic	>350	<30 000 (bDNA) or <50 000 (RT-RNA)	Consider starting antiretroviral therapy (opinions differ)
Asymptomatic	350 - 500	Any	Consider starting antiretroviral therapy ** DHHS guidelines A/B-II
Asymptomatic	>500	Any	Defer antiretroviral therapy (majority of experts) ** DHHS guidelines B/C-III

* See Table II.

** DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.[6]

Table II. Rating scheme for recommendations[6]

Strength of recommendation	Quality of evidence for recommendation
A: Strong recommendation	I: One or more randomised trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation	II: One or more well-designed, non-randomised trials or cohort studies with long-term clinical outcomes
C: Optional recommendation	III: Expert opinion

fosamprenavir, darunavir or saquinavir) plus two NRTIs. The preferred NRTI backbone can be either tenofovir/emtricitabine (Truvada) or abacavir-lamivudine (Epzicom) due to their lower pill burden, once-daily dosing frequency, and favourable side-effect profile. Abacavir/emtricitabine (Epzicom) should only be administered if HLA-B 5701 screening for abacavir hypersensitivity is negative. Zidovudine and lamivudine (Combivir) is considered an 'alternative' regimen because associated adverse events, such as gastrointestinal intolerance, headache, anaemia and lipodystrophy, make this combination less desirable. Tenofovir/ emtricitabine (Truvada) are the preferred agents used by many experts but tenofovir should be avoided in patients with a creatinine clearance <50 ml/min.

Although still used as first-line therapy in the public sector, stavudine is no longer recommended for the initial treatment of HIV-infected patients due to toxicity.

The latest DHHS[6] 'preferred' regimens for treatment-naïve, non-pregnant patients (Table I):

- Efavirenz/tenofovir/FTC
- Ritonavir-boosted atazanavir + tenofovir/FTC
- Ritonavir-boosted darunavir + tenofovir/FTC
- Raltegravir + tenofovir/FTC
- Lopinavir/ritonavir-based regimens are now listed as 'Alternative' (BI) except in pregnancy, where 2x/day Lop/Rit + AZT/3TC remains a 'Preferred' regimen (AI).

The rating scheme for recommendations is based on phase III randomised controlled trials (AI).[6]

NRTI combinations to avoid

- Zidovudine and stavudine due to pharmacological and *in vivo* antagonism.
- Lamivudine and emtricitabine, since these individual agents are essentially identical drugs with the same primary resistance mutation (i.e. M184V).
- Stavudine and didanosine due to overlapping mitochondrial toxicities such as peripheral neuropathy and lipodystrophy.
- Although still used as first-line therapy in the public sector, stavudine is no longer recommended for the initial treatment of HIV-infected patients due to toxicity (see SA Antiretroviral 2010 treatment guidelines).[7]
- The combination of didanosine and tenofovir is not recommended due to high rates of virological failure, blunted CD4 T-cell responses, and rapid selection of resistant mutants.
- There are insufficient data on the use of tenofovir and abacavir as combination.

NNRTI prescriptions

Nevirapine should be avoided in treatment-naïve women with CD4 >250 cells/µl or treatment-naïve men with CD4 >400 cells/µl. Nevirapine has a worse short-term toxicity profile than efavirenz, causing potentially life-threatening hepatitis and skin rash. Efavirenz is contraindicated in the first 28 days of pregnancy.

PI prescriptions

Long-term toxicities include hyperlipidaemia, hyperglycaemia and lipodystrophy (atazanavir is more lipid-friendly). Potential drug interactions should always be taken into account when prescribing a PI combined regimen, for example rifampicin, oral contraception, the statins, and even over-the-counter medication or traditional medicine. This might lead to treatment failure, drug toxicities or even the development of drug resistance.

When to switch

Treatment failure should be identified and managed promptly, with the goal of therapy being an HIV-1 RNA level below assay detection limits, even in heavily pre-treated patients. Genotypical testing is recommended (need a viral load of >1 000 copies/ml) as the preferred resistance testing to guide therapy in patients with suboptimal virological responses or virological failure while on first or second regimens (AIII). Patients failing second-line therapy should best be referred to experts for salvage therapy.

References available at www.cmej.org.za

In a nutshell

- The management of antiretroviral therapy is complex and is best when delivered by providers with specific training and considerable expertise.
- Post-exposure prophylaxis should be commenced within 1 - 2 hours after sharps injuries with at least two drugs and preferably adding a third drug, especially in case of high-risk injuries.
- The goals of antiretroviral therapy include viral suppression to a viral load <50 copies/ml; secondary goals are immunological restoration and prevention of HIV-related complications.
- Most guidelines recommend efavirenz or raltegravir or a ritonavir-boosted PI-based combination antiretroviral therapy as regimens of choice in treatment-naïve HIV-infected patients.
- To be in line with the 2010 South African antiretroviral treatment guidelines: tenofovir plus 3TC/FTC plus efavirenz (nevirapine as second option if efavirenz is contraindicated) would be the preferred first-line regimen for treatment-naïve patients.
- Tenofovir should be avoided in patients with a creatinine clearance <50 ml/min.
- Certain combinations of antiretroviral medications should be avoided either because of toxicity, lack of efficacy, or drug antagonism.
- The ultimate choice of regimen should be based on its potency, side-effect profile, convenience such as once-daily use and individual patient considerations, such as ability to adhere, concurrent medications, and other co-morbidities.
- Final selections of antiretroviral medications should take into account drugs to avoid during pregnancy and potential drug-drug interactions which are especially important with the use of protease inhibitors.
- The 2010 South African antiretroviral treatment guidelines will bring us closer to accepted international standards, but still fall short on one major issue and that is to initiate antiretroviral therapy for all patients with a CD4 count of 350 or below.