Do elite controllers need ART?

About 0.5% of people are able to control HIV infection with normal CD4 counts and undetectable viral loads (apart from occasional “blips” of up to 1,000 copies/mL). These people are called “elite controllers”.

A key question is: do elite controllers need ART? Common sense would suggest that ART would be unnecessary, but they have persistent immune activation, which has been associated with an increased risk of cardiovascular disease, cancer, and dementia. One small study including only 10 elite controllers showed an increased coronary artery calcification score on CT scan in elite controllers compared with HIV-uninfected controls - the score was similar in elite controllers and HIV-infected patients on ART.

A retrospective cohort study examined differences in the incidence of hospitalisation between 142 elite controllers and over 20,000 control patients on ART. On multivariate analysis the incidence rate ratio of hospitalisation of elite controllers compared with people on ART with a suppressed viral load was significantly higher (1.77 [95% confidence interval, 1.21–2.60]). Hospitalisation events in elite controllers were driven largely by cardiovascular and psychiatric events. It was noteworthy that hospitalisation incidence was somewhat higher in elite controllers than in patients on ART without suppressed viral loads, but the 95% confidence intervals of the incidence rate ratio of these groups overlapped with those of elite controllers.

These data strongly suggest that elite controllers need ART, and underscore the important role that immune activation plays in morbidity.

References

There is much progress in reducing vertical transmission of HIV. With the widespread introduction of lifelong combination antiretroviral therapy (ART) in pregnancy, risks of transmission in subsequent pregnancies will diminish even further, should adherence be maintained.

A key factor for early infant diagnosis (EID) was the development of polymerase chain reaction (PCR) to detect HIV DNA in peripheral blood mononuclear cells. This soon adapted to infants born to HIV+ mothers, and replacing cumbersome methods such as viral culture, p24 detection or still having HIV-specific antibodies at 18 months of age.

The original target age for EID was 6 weeks of age, to fit in with routine 6 weeks follow-up for all infants. In better-resourced settings, the testing often begins from 2 weeks of age, with a final test at 4 months of age. In the Children with HIV early antiretroviral (CHER) trial, a PCR was performed from 4 weeks of age and focused attention on the importance of EID in order to initiate ART as soon as possible. Initiating ART at a median of 7.4 weeks of age reduced the risk of death by 76% compared to starting ART at a median of 6 months of age for CD4 depletion or disease progression in infants with a baseline CD4 of ≥25%, the threshold for starting ART in 2006. During the screening phase, almost 20% of HIV-infected infants already had a CD4 percentage below 25% by 7 weeks of age.

The use of antiretrovirals to prevent mother-to-child transmission, even during the monotherapy era with nevirapine- or zidovudine-based regimens, has largely eliminated peripartum transmission, and most transmission now occurs in utero. In a study from Johannesburg where samples were collected from birth, almost 20% of HIV-infected infants who could have been diagnosed on day 1 of life had either died or were lost to follow-up by 6 weeks of age. A modeling study, considering immunization visits at 6, 10 and 14 weeks of age in South Africa, suggests a birth PCR and a second at 10 weeks of age as the best strategy to detect both early and later transmission. The birth PCR was initially recommended in South Africa for situations where risk of transmission is high but now is being phased in for all HIV-exposed infants and repeated at 10 weeks. A PCR is recommended 6 weeks after cessation of breastfeeding. The Mississippi baby, who, after starting ART on day 2 of life, stimulated interest in very early diagnosis and treatment. The mother discontinued giving ART at about 15 months of age, with subsequent loss to follow-up for 6 months. When first seen after defaulting care, the child was well with HIV only detected at the lower limit through highly sensitive tests. Unfortunately, after almost 2 years without treatment, virological relapse using conventional testing occurred and ART was restarted.

An emerging problem is that in the presence of antiretrovirals (ART), the sensitivity of PCR tests is compromised. A number of case reports have reported indeterminate PCR results, necessitating very careful follow-up. Recent data from the Breast Antiretroviral Nutrition (BAN) study in Malawi has provided worrying data on delayed diagnosis. In this study, infants born to HIV+ mothers were randomised to either enhanced standard of care (zidovudine and lamivudine for a week to infant and mother plus single dose nevirapine to both) or maternal ART versus infant nevirapine while exclusively breast-fed. Weaning occurred between weeks 24 and 28 and further follow-up until week 48. Nineteen of 28 infants diagnosed with HIV infection after 28 weeks, were studied. The median (interquartile range) time of first detection of HIV infection from their time of weaning was 83.5 (32.5–121) days, suggesting that a 6 weeks waiting period is too short. In a second study examining 9 of these infants who had stored peripheral blood samples, and using highly sensitive assays, not available for routine use, 6 infants were positive at 24 weeks, while the standard PCR test was negative. The median delay in detection between the ultrasensitive and standard assays was 18.3 weeks for the nevirapine arm, 15.4 weeks for the maternal arm and 9.4 weeks for the control arm. Although these data require validation with larger sample sizes, clinicians should be mindful of window periods and the limitations of current guidelines and tests.

**Conclusion**

Early diagnosis is essential when the risk of transmission is high. However, careful follow-up is necessary, and additional testing may be warranted.

**References**

The 2016 Annual Update Module is now available for AfA’s CPD-accredited Internet-based HIV management modular training programme!

Online modular training for doctors and other healthcare professionals in HIV medicine offers a practical solution to gain HIV management skills. It is particularly suitable for those working outside of the major centres. Individual modules or the full training programme may be completed. The course has been developed by Professor Gary Maartens, who is an acknowledged expert in HIV management and has participated in the development of HIV treatment guidelines both nationally and internationally. The modules cover the basics of HIV management and reflect current best practice, both nationally and internationally.

The annual HIV update module based on new guidelines and advances in HIV management is now available and, as with the other modules, is fully CPD-accredited.

The contents of the new update module include:

- Starting ART irrespective of CD4 counts: the evidence is in
- WHO recommends pre-exposure prophylaxis
- Post exposure prophylaxis - new guidelines
- New pro-drug of tenofovir
- Efavirenz: long term suicidality risk
- Should all people with advanced disease get TB therapy + ART?
- Diagnosing HIV in children
- No effect of NRTI resistance on 2nd line ART outcomes
- Do elite controllers need ART?

Registration on the course is free of charge and is open to all doctors as well as other interested healthcare providers.

Please go to [http://training.aidforaids.co.za/](http://training.aidforaids.co.za/) to register, using your professional council registration number and follow the simple instructions. If you do not have a professional council number your ID number may be used.
Aid for AIDS has recently updated its clinical guidelines regarding eligibility for ART initiation after the publication of 2 large landmark clinical trials that addressed the question of when to start ART in asymptomatic HIV-infected people: the START\(^1\) and TEMPRANO\(^2\) trials. Both these trials enrolled ART-naïve patients with high CD4 counts (in START all participants had a CD4 count > 500 cells/μl and in TEMPRANO 41% had a CD4 count > 500 cells/μl). Both trials involved randomisation to 1 of 2 strategies: immediate ART initiation, or to defer ART until the patient was eligible based on CD4 count or clinical criteria. Patients were followed for around 3 years in each trial, and the primary endpoint was a composite endpoint that included AIDS events, serious non-AIDS events and death.

Both trials demonstrated a statistically significant, approximate halving of events contributing to the primary endpoint when ART was started immediately. In TEMPRANO this benefit was largely attributable to reductions in incident TB and bacterial diseases. In START, the benefit was related to decreased AIDS-related events (including TB) and serious non-AIDS events (including cancer). The relative reduction in the rate of primary endpoint events was greater in START (57% reduction compared with 44%). However, the absolute benefit of immediate ART was greater in the TEMPRANO trial (conducted in Cote d’Ivoire) than in the START trial (which was conducted in countries across the world), because the event rate in the control arms was higher in the TEMPRANO trial (mainly due to TB and bacterial infections). This reflects the high co-infection risks that exist for individuals living with HIV infection in Africa, even with higher CD4 counts. No significant difference in mortality was observed between study arms in either trial.

There are two main concerns about ART initiation with CD4 counts > 500 cells/μl. First, the risk of adverse events could outweigh clinical benefits. Second, adherence could be lower in asymptomatic patients. In both trials immediate ART did not increase the risk of adverse events overall, and in both trials a high proportion of patients achieved viral suppression in the immediate arm.

The HPTN052 trial\(^3\) previously demonstrated that ART prevented onward transmission of HIV within serodiscordant couples suggesting that ART at HIV diagnosis for all may be an important strategy to help prevent the growth of the HIV epidemic at a public health level (“test and treat” strategy). However, such an approach would be difficult to justify if there was no individual benefit and potential individual harms from patients starting ART at high CD4 counts. What TEMPRANO and START have now demonstrated is that there is indeed individual clinical benefit with no signal of harm during ~3 years of follow-up.

Therefore CD4 count and clinical stage should no longer be a consideration in the decision to start ART. All patients diagnosed with HIV infection should be offered ART. For patients who are asymptomatic with CD4 > 350 cells/μl, a few weeks to a few months can be spent preparing the patient for lifelong ART before starting. But in patients with CD4 < 350 cells/μl or with a clinical indication for starting, there should not be undue delay in starting ART.

For more details regarding these trials please see the SA HIV Clinicians Society ART guidelines update: http://www.sahivmed.org.za/index.php/hivmed/article/viewFile/428/598

References


Pneumococcal pneumonia and invasive pneumococcal disease (IPD) are a major cause of morbidity and mortality in HIV-infected persons, irrespective of whether they are ART-naive or ART-experienced. Studies show an increase risk of IPD of between 10-300x that of HIV-uninfected persons, with a risk of recurrent IPD in those with HIV who have had a first episode of 25%. Despite a reduction in incidence in those that are on ART of 2-3 fold, HIV-infected persons on ART are still ~35 times more likely to have IPD than the general population.

Two vaccines against pneumococcus are currently in use in South Africa; 13-valent Pneumococcal Conjugate Vaccine (PCV-13; Prevenar) and 23-valent Pneumococcal Polysaccharide Vaccine (PPV-23; Pneumovax). PCV-13 replaced 7-valent conjugate vaccine (PCV-7). The advantage of conjugate vaccines over their polysaccharide counterparts is that conjugation of the polysaccharide with a protein induces T cell-dependent antibody responses, inducing B cell maturation, and memory B cell production. This infers long-lasting immunity as opposed to short-lived T cell-independent antibody responses of the polysaccharide vaccines.

The Advisory Committee on Immunization Practices (ACIP) recommends immunization of immunocompromised adults, including those with HIV infection, against pneumococcus. The suggested schedule depends on prior vaccination history and CD4 count:

1. No prior immunization against Pneumococcus with either PCV-13 or PPV-23
   a) A single dose of PCV-13 should be given irrespective of CD4 count, followed by a single dose of PPV-23 at least 8 weeks later.
   b) If the patient’s CD4 count is <200 cells/mm$^3$, then PPV-23 should be deferred until the patient has been started on antiretroviral therapy and achieved a CD4 count ≥200 cells/mm$^3$.
   c) A second dose of PPV-23 should be given five years after the initial PPV-23 dose.
2. For HIV-infected persons who have previously received one or more doses of PPV-23:
   a) A single dose of PCV-13 should be administered a minimum of 1 year after the last PPV-23 dose.

There are no contraindications to either PCV-13 or PPV-23 vaccination. The major adverse event from either is soreness at the injection site.

Until recently in South Africa, PCV-13 was only registered for use in the childhood extended programme of immunization or for adults ≥65 years. However, the PCV-13 label for South Africa has officially been approved by MCC to include the age expansion - for all age groups (6-17 yrs.; 18-49 years) and at-risks groups such as HIV, sickle cell disease and other immunocompromised patients.

References