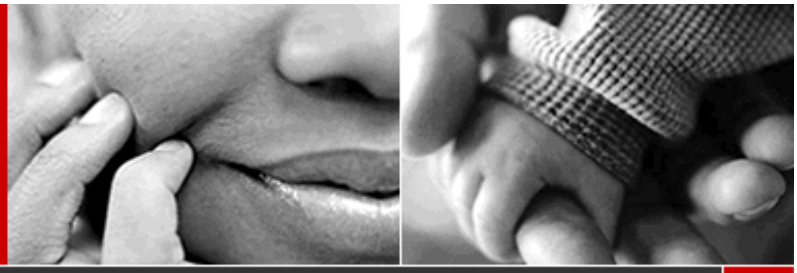

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Etravirine

Etravirine (Intelence™) is a second generation non-nucleoside reverse transcriptase inhibitor (NNRTI) recently registered for use in South Africa for treatment-experienced patients. Although etravirine has activity against most HIV strains that have developed resistance to the first generation NNRTIs (efavirenz and nevirapine), there is some cross-resistance. The number of NNRTI resistance mutations and the specific mutation (e.g. Y181I/V confers the highest fold change in susceptibility to etravirine) have been used to develop a weighting score to predict responses to etravirine-based ART. Using this score a study of 226 public sector patients in Johannesburg failing 1st line ART reported etravirine resistance mutations in 39%, with high level resistance in 9%.[1]

A phase 2 randomised controlled trial comparing etravirine with an investigator-selected protease inhibitor (PI) in patients with NNRTI resistance who were naïve to PIs was stopped prematurely as etravirine was significantly inferior to PIs.[2] For this reason etravirine is not recommended for use alone with NRTIs in treatment-experienced patients and should always be combined with a PI. The pivotal phase 3 trial (the combined report of the identical DUET 1 & 2 studies) compared etravirine with placebo in 1,203 patients with at least one NNRTI resistance mutation and at least 3 primary PI resistance mutations who were commenced on a salvage darunavir/ritonavir-based regimen.[3] The etravirine arm performed significantly better than placebo, with 61% versus 40% of patients having a viral load <50 copies/ml at week 48.

Etravirine is generally well tolerated. Hypersensitivity rashes occurring in the first few weeks of therapy are common, with a frequency and severity similar to efavirenz. Severe hypersensitivity reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, or systemic hypersensitivity with constitutional symptoms and organ dysfunction) may occur. Liver enzymes should always be checked if a rash develops and etravirine must be immediately discontinued if the ALT is significantly elevated, or if there are symptoms of hepatitis. If the rash is mild and there are no features of systemic hypersensitivity etravirine should be continued with careful observation – the rash settles in most patients. There does not seem to be an increased risk of rash in patients who have developed rashes on first generation NNRTIs. Hepatitis without a rash may also occur.

Etravirine is involved in more drug interactions (mostly involving interactions with cytochrome P450 enzymes) than efavirenz or nevirapine. Like the first generation NNRTIs, it is an enzyme inducer. The package insert or other drug interaction resources should always be checked before prescribing other drugs. Of note is that it cannot be used with rifampicin. There is limited data on the use of etravirine with rifabutin when given together with a PI. Therefore in patients with tuberculosis it would be best to avoid etravirine. Etravirine should not be used with unboosted atazanavir as there is a bi-directional interaction. Etravirine may be used with caution with boosted atazanavir.

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AfA recommends the use of etravirine in salvage therapy, always together with a PI (usually darunavir/ritonavir). The dose is 200 mg 12 hourly with food. One drawback to its use in salvage therapy is that genotypic resistance tests are usually done after failure of 2nd line protease inhibitor-based ART and the NNRTI mutations from 1st line ART may no longer be detectable. Therefore complete information on etravirine resistance may not be available.

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Potential Cure of HIV in an infant – The Mississippi child – What can we learn? Can we already change our practice?

At the recent 20th Conference of Retrovirology and Opportunistic Infections (CROI) held in Atlanta, Georgia in February 2013, Dr. Persaud and colleagues presented a well-documented case of probable cure in a HIV-infected infant.[1] A mother was diagnosed as HIV-infected by rapid test when presenting in labour in Mississippi, USA. The delivery was precipitous without opportunity for maternal ART. Her viral load was 2423 copies/mm^3 and CD4 count was 644 cells/mm^3. Her virus was sub-type B, the dominant North American clade. The baby's HIV status was confirmed by 2 independent tests, a HIV DNA PCR at 30 hours of age and a HIV RNA viral load of 19812 copies/mm^3 an hour later.

The infant was immediately commenced on ART consisting of nevirapine (NVP) at full therapeutic dose (instead of a daily "lead in" dose for 2 weeks), with 3TC and zidovudine. Lopinavir-ritonavir (LPV/r) was substituted for NVP at a week of age. HIV RNA was detected in the infant's plasma on 3 more occasions until below detectable limits (<48 copies/mm^3) at 4 weeks of age. Viral load remained undetectable until 18 months of age when the infant was lost to follow-up and discontinued ART. Eight months later, when follow-up resumed, the infant was thriving. Viral load was undetectable, the standard HIV DNA PCR was negative, the CD4 was within normal range for age and HIV antibody was undetectable. Ultrasensitive methods revealed 4.2 HIV DNA copies per million peripheral blood mononuclear cells and a viral load of 1 HIV RNA copy/mm^3.

Additional investigations showed that the HIV was sub-type B, the dominant North American clade, HLA linkage confirmed relatedness between the mother and infant. The mother did not have the CCR-5 HIV co-receptor delta 32 deletion previously associated with cure in the "Berlin patient".[2]

Studies of limited ART followed by ART interruption after acute infection in adults supports this concept. In the randomized Short Pulse Anti-Retroviral Therapy at Seroconversion (SPARTAC) study, early limited ART for 48 weeks followed by interruption was associated with higher CD4 counts and longer time off ART compared to standard of care or ART for 12 weeks.[3] A French cohort study recently reported on 14 adults, treated for a median of 36 months and able to control HIV replication for a median of 89 months off ART. They estimated that 15% of those treated early in acute infection, might show similar control.[4]

In children, the final results of the CHER trial confirmed the safety of early limited ART in infants commencing ART at a median of 7 weeks of age with a trend to better outcome in children treated until the 2nd rather than the 1st birthday.[5]

Timing of HIV transmission and reliability of HIV DNA PCR at 6 weeks of age

With all of the improvements in prevention of mother to child transmission (PMTCT), transmission has been impressively lowered from approximately 30% to 3.5% in South Africa.[6] Late presentation and delayed access to ART are major risk factors for transmission. A recent South African study showed that a PCR on day 1 of life identified 29/38 (76%) of HIV infections in infants. The high proportion with PCR positive on day 1 in this study is because women had received PMTCT. The PMTCT regimen allowed zidovudine (AZT) from 28 weeks gestation and single dose of NVP in labour. Babies received sd NVP and AZT for a week. "Adequate" PMTCT, defined as receiving AZT for >4 weeks antenatally, was given to 79% of mothers in the cohort. By 14 weeks of age, 13 (45%) of these infants had either died or were lost to follow-up.[7] This study both confirms the value of a PCR on day 1 of life and suggests a poor outcome for *in utero*-infected babies. The timing of *in utero* infection is also of concern and probably more common in late than early pregnancy. Although currently defined as a positive PCR in the first 48 hours of life,[8] *in utero* infection has already been described at 15 and 20 weeks gestation.[9,10] Early *in utero* infection is likely less susceptible to possible cure than in late pregnancy.

Reasons for "cure" in the Mississippi Baby

The mother had an extremely low viral load at delivery and the baby probably received a low inoculum late in pregnancy. The diagnosis was confirmed within 31 hours, with immediate initiation of ART (including full dose NVP). NVP appears to have high penetration into the central nervous system,[11] one of the HIV sanctuary sites. The most important component was early diagnosis with ART implemented as prophylaxis by 31 hours of age. The relative importance of NVP versus LPV/r is unknown. NVP has good penetration into all body compartments, while the FDA have recommended that LPV/r not be given in the first 2 weeks of life due to concerns of toxicity.

How should we respond to the Mississippi Baby for babies at high risk for vertical transmission?

The British HIV Association (BHIVA) already has guidelines in place for babies born to mothers at high risk of HIV transmission and recommends triple therapy for babies in the 1st 72 hours of life under the following circumstances[12]:

1. Mother diagnosed HIV infected after delivery
2. Detectable maternal viraemia (>50 HIV RNA copies/mm^3) at delivery, regardless of maternal ART status
    a) Delivery before complete viral suppression is achieved (e.g. starting ART late or delivery premature)
    b) Viral rebound with or without resistance, with or without poor adherence
    c) Premature delivery before starting ART or late presentation

Response

- Better prevention
    - Use triple ART in high risk infants
- Very early diagnosis
    - Diagnostic PCR in 1st 24 hours of life (collect 2 specimens an hour apart: retain 2nd specimen to confirm a positive result: Do not use cord blood as easily contaminated by maternal blood)
        - If negative
            - Continue triple ART for 4 weeks
            - Repeat diagnostic PCR at 6 and 12 weeks
        - If positive
            - Do viral load in the neonate
            - CD4, FBC, AST
            - Continue triple ART

Which ARTs should we use?

There is good rationale for the regimen chosen for the Mississippi baby. NVP probably has better central nervous system penetration [13,14] but over a longer period, LPV/r has more durability[15].

For a mother who has failed 1st line ART or is non-adherent, consult an expert.

We suggest the following:

- Initiate AZT, 3TC and NVP for all 'high risk' neonates on day 1 or as soon as possible for 4 weeks
- Start LPV/r as soon as positive PCR obtained
- For HIV-infected babies, adjust dosages after a month (for low birth weight infants, consult an expert)

Medication	Dosage	Comment
Zidovudine (AZT)	**Oral** *Term* (>34 weeks): 4 mg/kg bid *Premature* (30–34 weeks): 2 mg/kg bid for 2 weeks: then 2 mg/kg tds for 2 weeks *Premature* (<30 weeks): 2 mg/kg twice daily for 4 weeks **Intravenous** *Term:* 1.5 mg/kg 6 hourly *Prem:* 1.5 mg/kg 12 hourly	
Nevirapine (NVP)	2 mg/kg daily for 1st week then 4 mg/kg daily for 2nd week Use 4 mg/kg daily for 2 weeks if mother received NVP >3 days	
Lamivudine (3TC)	2mg/kg bid	
Lopinavir/r (LPV/r)	>2kg: 300 mg/m^2 bid 1–2 kg: 40 mg bid 2–6 kg: 80 mg bid	• Can use Surface Area • Concern about safety until 42 weeks post-conception (2 weeks of age in term infants) • Monitor for arrhythmia and hyperosmolality

Should ART be discontinued in the child after sustained viral suppression?
Although the CHER study has confirmed the safety of treatment discontinuation after early primary ART under close supervision, this should NOT be attempted outside of an ethically approved clinical study.

What should be the frequency of HIV PCR for the infant at high risk of acquiring vertical HIV?
The PCR should be repeated at 6 and 12 weeks of age. (ART could reduce the sensitivity of a diagnostic PCR, which should be after a reasonable period in presumed HIV-uninfected infants), as was noted in a recent infant post-exposure prophylaxis study in mainly unbooked mothers[16]. (Note: for breastfed infants, NVP should continue in HIV-uninfected infants until the infant has been fully weaned or until the mother has a viral load below detectable limits on ART. Adjust dose for increasing weight).

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Use of Pre-Exposure Prophylaxis

Pre-exposure prophylaxis (PrEP) refers to the administration of antiretroviral medicines before a possible exposure to HIV. This distinguishes it from post-exposure prophylaxis (PEP), which is given after an occupational or sexual exposure. Oral PrEP is one of a range of preventative measures, which include condoms.

Tenofovir (TDF) alone or in combination with emtricitabine (FTC), has been most extensively studied for PrEP, first showing dose-dependent efficacy in the macaque following mucosal or systemic challenge. Thereafter, 6 placebo-controlled RCTs studying oral PrEP have either been completed or are near completion:

Trial	Study Group	Intervention	Result
iPrEX	2499 MSM/ Transgender Women	Daily TDF-FTC vs placebo	Reduced HIV acquisition by 44% [95% CI 15-63, p=0.005]
FEM-PrEP	2120 women	Daily TDF-FTC vs placebo	Stopped due to futility. Efficacy estimate 6% [-52-41%, p=0.8]
TDF2	1219 heterosexual men and women	Daily TDF-FTC vs placebo	Reduced HIV acquisition by 62% [22-83%, p=0.01]
Partners -PrEP	4758 uninfected partners of HIV-infected persons	Daily TDF-FTC or daily TDF vs placebo	Reduced HIV acquisition by 67% (TDF) or 75% (TDF-FTC). No statistical difference between TDF and TDF-FTC
VOICE	3012 women	Daily TDF-FTC or daily TDF vs placebo	Oral TDF arm discontinued by DSMB* due to lack of efficacy. TDF-FTC not protective.
Bangkok Tenofovir study	2413 injection drug users	Daily TDF vs placebo	Ongoing

*Drug and Safety Monitoring Board

Two common threads are evident when analysing these trials. Firstly, despite intensive concomitant interventions such as individualized adherence counselling, regular study visits and strong and continuous positive feedback, adherence was universally poor. However, whether adherence was measured by pill counts or drug levels, it correlated with efficacy in preventing HIV acquisition. A difference in adherence rates between studies is one of the key reasons for the different outcomes. Therefore, PrEP certainly does work, but adherence is poor, even in the setting of a rigorous clinical trial. A widespread public health intervention of oral PrEP is very unlikely to be effective because adherence can be expected to be even worse than it has been in the rigorous setting of clinical trials.

The National Strategic Plan on HIV, STIs and TB 2012-2016 does not recommend oral PrEP, but rather calls for further research targeted at high-risk groups. However, as the aim of oral PrEP is to reduce HIV acquisition, and the evidence indicates that when PrEP is taken, it is effective, its use should be individualized. Whether a patient falls into a high-risk group or not, PrEP should be available if requested.

Prior to prescription of PrEP, HIV seronegativity must be confirmed and a screening test for hepatitis B (HBsAg) should be undertaken. HIV testing should be performed 3-monthly and persons taking PrEP should be encouraged to return should they experience any symptoms compatible with HIV seroconversion. Renal function should be monitored during PrEP at 1, 4 and 12 months and annually thereafter. Full adherence counselling and promotion of other preventative measures particularly condoms, should accompany any prescription for PrEP and follow-up visits should be planned to reinforce prevention measures.

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20th Conference on Retroviruses and Opportunistic Infections

This conference was held in Atlanta, US, from 3-6 March 2013. Over 4000 HIV researchers from around the world attended and findings from over 1000 studies were presented. Two of the major findings presented (the functional cure of HIV in a young child and the final results of the VOICE PrEP trial) are discussed elsewhere in this newsletter. Here we discuss two studies that may impact on ART treatment options in the future.

Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir. In comparison with the tenofovir prodrug that we currently use (TDF = tenfovir disoproxil fumarate) it results in 90% lower plasma tenofovir levels and a 5-fold increase in the active intracellular tenofovir disphosphate levels, at much lower doses. In a phase 2 trial comparing TAF vs TDF in antiretroviral regimens with 24 week follow-up [1], TAF had comparable efficacy in terms of virological suppression (87% vs 90% had HIV VL < 50 copies/ml at week 24) and statistically significant less impact on eGFR and bone mineral density than TDF. TAF represents an option to TDF for the future. By reducing the plasma level of tenofovir it may reduce side effects, but this needs to be tested in a larger phase 3 trial.

Maturation inhibitors are a novel class of antiretrovirals in development. They directly target the gag protein and disrupt its processing by the protease enzyme, just before the newly formed virus buds off the cell. This disruption results in the formation of non-infectious viral particles thereby stopping onward viral replication. The first candidate in the class (beviramat) showed great promise and progressed to early clinical phase development, but development was stopped when it was found that 50% of HIV strains were intrinsically resistant due to a single polymorphism in gag. Twenty 2nd generation maturation inhibitor candidates have now been developed by modifying the chemical structure of beviramat. These candidates were shown to have antiviral activity against beviramat-resistant strains *in vitro* re-opening the possibility that active drugs from this class may be a treatment option in the future [2].

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In an attempt to encourage and facilitate early registration of HIV positive members, AfA has devised a ONE PAGE, pre-HAART application form.

This form must only be used for patients who do not yet qualify for antiretroviral therapy but who need to register on the AfA programme to gain access to HIV benefits offered by their medical aid scheme.

Please note that the 4 page application form still needs to be completed in the following cases:

- pregnant patients qualifying for PMTCT
- patients qualifying for ongoing ART