Brief Report: 9th Bangkok Symposium on HIV Medicine

I attended the 9th Bangkok Symposium on HIV Medicine, organized by HIV-NAT from 18-20 January, with funding from IHPCP. This was a meeting primarily focussed towards medical professionals from around Asia. I think I was probably one of the only activists present. There were more than 400 participants, with 16 from Indonesia. Besides the 'IHPCP/ASA Group', there was also a group from PDPAI headed by Prof. Samsuridjal.

The mornings of each of the three days were taken up with plenary sessions (six on each day), while the program for the two afternoons offered a choice of sessions presenting case studies. Sadly the level of participation in the case studies I attended was relatively low. Almost all sessions were of a very high standard, very practical and presented clearly and in terms appropriate to developing country participants, with almost all providing 'take-home messages'. In this report, I will try to discuss those messages which impacted most strongly on me, and which I feel are most applicable to the Indonesian situation.

1. Primary infection. I had been under the impression that viral load started to increase rapidly immediately after infection. I learned that it actually starts some two weeks following infection. As a practical point in the developing world, I don't think the case was made strongly for greater efforts to identify infection in the primary stage, although of course we do need to try to find cases earlier, and if doctors are more suspicious when patients present with flu-like symptoms, this might assist in that process.

Several speakers referred to a recent study that indicates that HIV very quickly moves to infect and deplete CD4 cells in lymphoid tissue in the gut. It was noted that 70% of CD4 memory cells are located in submucosa in the gut, compared with 1% in the blood. This suggests that HIV causes immune deficiency as a result of the host's immune response, rather than by directly infecting and killing CD4 cells – less than 1% of CD4 cells actually get infected by HIV.

2. Initiation of ART; when to start and what to start with. Don't think there was anything new on the first (when to start). The current guidelines seem to be appropriate. However, several ideas on drugs/doses came out of presentations, case studies and discussions in corridors. Regimens consisting of two NRTIs and one NNRTI continue to prove most appropriate, with a preference for efavirenz, even though nevirapine seems more or less equivalent. Several doctors are using lower doses of d4T (20mg with low body weight), and most seem to avoid 40mg even for higher body weight. AZT is often started at 200mg rather than 300mg, especially for low body weight or where there are signs of anaemia. We should consider a change to 250mg (which is WHO-approved) to reduce cost and side effects. In cases of anaemia with AZT, consensus seems to favour a temporary change to d4T, with a re-challenge of AZT once Hb has returned to normal after 3-6 months. More than 20% of Thai patients experience lipoatrophy at 48 weeks on d4T; an early change to AZT can avoid this.

There was discussion on staggered start to therapy, with NNRTIs started two weeks after NRTIs. This reduces overlapping side effects, and avoids having to stop NNRTI after a couple of weeks in case of toxicity from NRTIs, which could lead to NNRTI resistance. It could also reduce likelihood of IRIS (see below), since this seems to be stimulated by rapid CD4 increase. One presentation noted that resistance to 3TC only appears after 3-4 weeks of dual therapy, so this should be safe.

There is evidence that a backbone of tenofovir (TDF) and emtricitabine (FTC) is better than the standard AZT and 3TC. However this option is unlikely to be affordable for first line in Indonesia for the next few years.

An alternative starting therapy discussed is highly unusual: d4T + TDF + 3TC. This should be relatively cheap if special pricing of TDF can be accessed, and spares both NNRTI and PI. But its major benefit is that, in case of failure, the resistant mutants (K65R and M184V) will still allow (even enhance) AZT replacement of d4T with no other changes. Even prolonged use after failure will not cause development of other more concerning mutants (TAMS) as would normally be the case.

In cases of TB coinfection, interaction with rifampicin was discussed. Almost all boosted protease inhibitors (PIs) have their levels much reduced by rifampicin, precluding their use. Efavirenz levels are also reduced, but studies in Thai patients have shown standard dose remains effective. Nevirapine levels are also reduced, but studies have shown that standard dose is effective for 86% of patients. How do we identify the other 14% in advance? General recommendation remains to use nevirapine if no other options available.

3. Stopping NNRTIs. Because efavirenz and nevirapine have long and variable half-lives, stopping them at the same time as the NRTI backbone will almost certainly result in NNRTI resistance. There is growing consensus that NNRTI should either be stopped at least seven days before the backbone, or (better) the NNRTI replaced with a PI for a week before stopping.

4. Treatment Failure. There was an excellent presentation on the pathways for development of resistance. Almost certainly continued treatment AZT + 3TC backbone regimen after failure will mean that no other NRTIs will retain efficacy. Failure of any NNRTI regimen precludes use of any currently available NNRTIs. This really leaves only dual boosted PIs, with lopinavir, saquinavir and ritonavir boosting (Kaletra + saquinavir) probably the best option.

Several speakers noted that most resistant mutants are less fit, some considerably so. Thus there can be benefit in maintaining the resistant mutants. This is particularly appropriate with the M184V mutant resulting from 3TC resistance, which increases efficacy of AZT; many are now suggesting continued use of 3TC, for example with the dual boosted PI regimen discussed above, to maintain this pressure.

5. Cohort Data. It became clear from several presentations that Thailand has been very effective in accumulating useful data on patient history/outcomes and the associated costs. In the Indonesia group we discussed the need to strengthen our response in this regard. This will help us to determine cost-effectiveness and identify appropriate strategies.

6. Mother-to-Child Transmission. Much of the discussion here was around the risk of nevirapine resistance following single dose for prevention of transmission. It is now clear that resistance occurs in a vast majority of cases. For this reason, latest guidelines suggest use of AZT + 3TC for seven days to cover the nevirapine ‘tail’. There is concern that this could result in resistance to 3TC, but other trials have suggested that this is unlikely to develop in such a short time.

One speaker also noted that use of ART had reduced transmission rates to below 2%, and questioned whether C-section has greater risk than benefit if ART can be used. Note: ART throughout pregnancy would be much cheaper than C-section!

7. Paediatric Treatment Strategies. Unfortunately very little of this session actually discussed paediatric treatment, and presented little new. There was some discussion on immunotherapy, with one possible candidate being green tea.

8. Hepatotoxicity. There was frequent reference to this side effect, particularly in the case studies. Most experts advised only monitoring elevated liver enzymes, even at more than five times upper limit, as long as there are no symptoms. Generally they will resolve in time. When I noted that Indonesian doctors usually prescribe herbal ‘hepatoprotector’ combinations, no one

took it seriously! But no other alternatives were offered. Could we not do some studies to validate frequent use of these?

9. Mycobacterium. Several presentations on HIV/TB coinfection. General agreement that PPD test provides little benefit. New TB Spot blood test may be more useful, but not currently approved for use in HIV positive persons, and not useful for diagnosing MAC. Speakers were doubtful of benefit of mass izoniazid preventive treatment (IPT), particularly where TB is endemic, because of high risk of reinfection; it would need to be given for life, and that is not practicable. ART is more effective. However, one speaker did agree that IPT should be given to PLHAs exposed to active TB for more than eight hours, e.g. if living in the same household as a confirmed case.

Twice weekly TB regimens have been proved to lack efficacy in people with CD4 less than 100. It is assumed that three times a week is as effective as daily in this group, but has yet to be proved.

A couple of case studies noted that we should not ignore the possibility of MAC if CD4s are low, particularly in unexplained febrile cases – this was a more frequent cause of prolonged fever than TB in one Thai study.

Frequent aspiration of swollen lymph nodes is necessary to avoid bursting.

10. Neurological Manifestation. While case studies were interesting, they featured frequent use of CAT and MRI scans, which will probably not be possible in Indonesia. Relatively frequent occurrence of cryptococcal meningitis was noted. This can be identified relatively easily and cheaply from antigen in a blood sample and from the headaches at front of head that are not improved with paracetamol.

11. IRIS (Immune Reconstitution Inflammatory Syndrome). It was noted that there is no case definition of IRIS, that it could take two forms (reactivation or unmasking), and that there is no evidence base for the use of corticosteroids; indeed sometimes this can make things worse. It normally occurs in the first three months after starting ART, but can occur up to two years later.

12. Circumcision. Several references to the recent evidence of the protective effect of circumcision. One interesting comment was that there is some evidence in retrospective data from Uganda that suggests that circumcised males may be less infectious.

13. New Drugs. There is now much doubt that the CCR5 inhibitors currently in development will actually reach the market – they all seem to be falling down in trials. But a couple of new NNRTIs (TMC-125 and TMC-278) that are effective against resistant mutants show hope, although while TMC-125 did well in trials in the US, it failed in trials in Thailand.

14. Viral Hepatitis. Noted that incidence of liver disease mortality relatively low, and it appears that ART does help stabilize liver disease. However, there is evidence that d4T probably increases fibrosis. There is little evidence that 3TC in ART has much impact on progression of hepatitis B, but there have been no studies of the effect of TDF on HBV-infected PLHAs. It was noted that “there is the beginning of evidence that TDF can make a major change in HBV”, with no viral breakthrough as a result of resistance after three years.

15. ART for IDUs. Some limited discussion on this. But it was noted that “Adherence among IDUs is better than many clinicians assume.”

16. Role of Protease Inhibitors. Clearly there is almost no role for unboosted PIs now – nelfinavir was rarely mentioned. The main drugs we are likely to see are lopinavir/r (Kaletra) and saquinavir/r, although others may come along later. These give better results, less toxicity and negligible resistance in naïve patients. However, they do still give rise to metabolic

complications, and these must be carefully monitored. One concern is the 2nd line regimen option of ddI, tenofovir, and lopinavir/r. This is now a 'not-recommended' combination, although still frequently used, particularly with concern over elevated side effects of ddI. With careful monitoring these can be anticipated and avoided. The other concern is that lopinavir/ should be taken with food, while ddI should be taken on an empty stomach. However, if this gives rise to problems with adherence, better to take ddI with the other drugs with food, rather than miss the dose; the impact of this was said to be probably minimal.

17. Side Effects. Other than those covered above, special emphasis was placed on lactic acidosis and insulin resistance. The former, while rare, can build up very rapidly and can quickly be fatal, and doctors should always consider this if adverse effects are experienced some time after therapy has started, especially with d4T. I suspect some of our cases of 'sudden death' may result from undiagnosed lactic acidosis. Insulin resistance is more common with protease inhibitors, and can give rise to heart problems.

Also discussed frequently was lipodystrophy, a concern that is likely to grow in Indonesia. While lipohypertrophy (build up of visceral fat, e.g. 'buffalo hump') is often quoted, there is evidence that this is actually no more common in HIV-positive people (on or off ART) than HIV-negatives. More concerning is lipoatrophy (loss of fat, usually in cheeks and arms/legs), with evidence that this is exacerbated by d4T, low viral suppression/CD4, and increasing age (PIs have less effect compared with lipohypertrophy). While this can result in elevation of triglicerides and insulin resistance, the much bigger concern is psychological, with implications for adherence. Switching from d4T to AZT, or (better) ABC or TDF, or even to ddI can help. Treatment with uridine has also been shown to be effective in regaining the fat.

18. Dementia. This continues to be seen, and indeed has become more common, in the ART era, as people live longer. There are not as yet any good therapies, but changing to drugs that do a better job of penetrating the blood-brain barrier may help.

19. Pre-exposure Prophylaxis (PREP). We heard of the problems faced by the intended trials of tenofovir among vulnerable populations (sex-workers and IDUs), taken daily to prevent HIV infection. Prophylaxis of this nature is very common (malaria, TB, IOs), so it is not clear why the 'activists' resist it. It was agreed that we need to do a better job of explaining the logic. But also we should not limit trials to just one drug; almost any drug that interferes with the early life history of HIV could be effective, with 3TC an especially good candidate given low toxicity. However, PREP must be restricted to HIV negatives (how?), or we will get transmission of viral strains resistant to the PREP drug. Ideally we should reserve one class of drugs specifically for this purpose.

20. Structured Treatment Interruptions (STI). This talk was dominated by the just-announced suspension of the SMART trial, a very large clinical trial looking at CD4-guided STIs. Given its similarity with other successful (if smaller) trials, it is not clear why this failed, and this will need to be further evaluated. This should once again remind us that STIs should only be carried out in a research environment, with very careful monitoring; STIs are in no way ready for 'prime time' in normal clinical practice, and those on ART must be very cautious in interrupting therapy without the full agreement and support of the doctor.

Chris W. Green, 22 January 2005