1. Overview of selected references

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2. Overview of technical notes

- **Operational PMTCT programmes**

  **Impact of PMTCT on HIV-free survival rates**

  *Note appearing in HIVCare_05_07 and commenting to the following paper:*

  We are commenting here on the above study published in AIDS looking at the operational effectiveness of PMTCT programmes in South Africa. This article is particularly interesting in the fact that most previous operational studies looking at the effectiveness of PMTCT programmes have been centred on pilot programmes which were often hospital based, showing short term follow up (6-16 weeks) and which did not measure HIV transmission and or infant death. In this research, sites were operational rural or urban sites and the study was designed to look at the longer term follow up of PMTCT programmes with the main outcome of interest being HIV free survival at 36 weeks. Secondly the results of this study suggest that if benefits of PTMCT programmes are to be realised than attention must be focused on also strengthening the health care infrastructure especially in disadvantaged areas with low resources and poorly functioning health services.

  This recently published research was carried out in 3 chosen sites among 18 pilot sites of the South African PMTCT program following 665 HIV positive mothers and infants. The sites were chosen to reflect difference in circumstances (prevalence of antenatal HIV prevalence, socio-economic status and rural or urban settings). An urban-periurban with relatively high socio-economic profile and a relatively well functioning public health care system (Paarl) with an antenatal HIV prevalence of 9% was compared to a rural site in one of the poorest regions with a antenatal HIV prevalence of 28% (Rietvlei) and a periurban site considered as intermediate with an antenatal HIV prevalence of 47% (Umlazi).

  The authors reported substantial differences across sites with regard to maternal and infant characteristics, quality of care and infant feeding practices with the rural site in the poorest region showing as expected the poorest indicators in terms of quality of care as measured by antenatal visits, syphilis screening, postnatal visits and immunisation rates. When the authors looked at the outcome of interest the differences seen in cumulative HIV transmission at 36 weeks across sites were not statistically significant (P=0.07) but infant mortality was significantly higher in the rural resource poor site (P=0.0005). The composite indicator was significantly different across sites for HIV free survival rates at 36 weeks of age of 84% for the most advantaged site, 73% for the intermediate site and 64% for the poor rural site (P=0.0003). Only two independent risk factors for HIV free survival transmission and or infant death in the multivariate analysis were found; maternal viral load and prematurity. But even after controlling for these two factors, the site difference still remained statistically different. This led the authors to conclude that established risk factors do not explain differences in HIV free survival rates between sites (maternal viral load was actually highest at the site with the best HIV
survival rate). When they used models to analyse this data, regression analysis suggested that a mother in the most disadvantaged site with similar viral load, gestational aged baby and infant feeding practices was still more than twice as likely to have an HIV positive infant or see her child die by 9 months. This led the authors to suggest that the difference across sites in HIV transmission and or infant death could only be explained by the difference in quality of healthcare system services As it has been suggested by McCoy when describing the pitfalls of rapidly expanding ART programs or by Peeling et al when looking at the uptake of syphilis screening in Haiti in maternal services, their findings also suggest that the addition of new vertically led interventions such as PMTCT programmes to already under-resourced and poorly functioning health systems may not lead to improved HIV related health indicators. Recently MSF has made a well publicized appeal to donors recommending that adequate human capacity is essential for the success of ART programmes in low income countries and that health care systems need to be strengthened and specific attention given to the provision of additional resources such as adequately paid staff and funding to poor-functioning health care systems in disadvantage areas whilst avoiding to divert resources from other important public health issues.

The authors conclude by suggesting that new programmes such as PMTCT should be designed from the start for “active catalysis” of broader health system development rather than a narrow vertical intervention.

References:
1. Leroy et al. AIDS 2005; 19:1865-1875
4. MSF http://www.msf.org/msfinternational

Postnatal transmission of HIV

Infant morbidity and mortality data in the context of replacement feeding

Note appearing in HIVCare_03_08 and commenting to the following paper:

In the issue of Plos Medecine of January 2007, Becquet and colleagues have published an original study looking at two year morbidity and mortality data in the context of alternative infant feeding interventions aimed at reducing mother to child transmission (MTCT) in an urban setting in Africa. In the midst of the continuing debate over infant feeding practices for children born to HIV-infected mothers in resource constrained settings, this article brings important information on when replacement feeding might be safe for babies. The primary finding of this study provides the best reassurance to date that, when appropriate support is given, the long term morbidity and mortality outcomes among short-term breastfed and formula fed infants are comparatively similar as opposed to the standard more prolonged breastfeeding.

In the light of the UNAIDS guidelines which recommend that HIV-infected women should use replacement feeding only when it is AFASS (acceptable, feasible, affordable, sustainable and safe) or otherwise practice exclusive breastfeeding for the first six months or until AFASS criteria are met, this study provides information on the safety of two alternative options. Whereas new evidence has recently shown that early cessation of breastfeeding (BF) was associated with increased morbidity and mortality in infants in completed (Malawi, Botswana) and ongoing studies (Kenya, Uganda and Zambia), data on morbidity in an environment where women were asked to choose one of the two feeding options and offered support (free formula, transport and health care provision) and counselling for either one is here being shown. The authors compared formula-fed (FF) to BF-mothers (early cessation of BF from 4 months) in Abidjan, Côte d'Ivoire and found that severe adverse events amongst infants were similar in both groups. Of the 557 live born children, 47% were BF for a median of 4 months whereas 295 were FF. The 2-year probability of presenting with a severe adverse event (hospitalization or death) was the same among FF (14%) and short term BF children (15%) (Adjusted HR: 1.19, CI: 0.75-1.91 p=0.44). Even though FF infants had a slightly higher increased risk of diarrhoea (27 versus 22 cases per 100 persons year) and acute respiratory disease (9 versus 6 person-year) and BF children higher rates of malnutrition (14 versus 10 per 100 person-year), this did not however translate over the 2 year period
in higher incidence rates of hospitalisation or mortality. The authors also compared the mortality with a historical trial done in the same area with no specific infant feeding counselling; infants were long-term BF in this trial, and the MTCT rate was therefore much higher. Compared to HIV-negative children, there was no difference in risk of death among the FF and short-term BF babies from this new cohort.

These modified feeding practices were proposed with appropriate conditions (provision of nutritional counselling for all women, free provision of breast milk substitutes, and assurance of access to clean water) in association with frequent follow-up, infant growth assessment as well as morbidity assessment. This translated into a high rate of retention into care with 88% of expected follow-up completed. These conditions do not always apply to other settings in Africa and therefore the authors have only pointed out that replacement feeding or short term BF is safe within a specific package of interventions. These data help pave the way to more individual-oriented recommendations helping to promote informed and free choice of infants feeding methods for HIV-infected mothers. The authors believe that HIV-infected women should be given specific guidance in selecting the option most likely to be suitable for their individual situation in PMTCT programs even in resource-constrained settings.

References:

Maternal disease progression and breastfeeding

Note appearing in HIVCare_03_07 and commenting to the following paper:

Othieno et al have published in the 15th of January issue of JID, a study regarding the association between breastfeeding and maternal disease progression and death, which is an issue with important implications for public health policy. As Wilfert and Fowler \(^1\) point out in the editorial commentary in the same issue, it is of great importance to ascertain whether breastfeeding compromises maternal health in the presence of HIV infection. Two recent analyses in Kenya and South Africa regarding breastfeeding and mortality among women infected with HIV-1 have produced conflicting results and therefore Othieno et al’s results are reassuring as they found no association of breastfeeding with increased maternal mortality when appropriate care was available.

In a previous Kenyan clinical trial, Nduati et al \(^2\) had found that breastfeeding by HIV-1 infected women resulted in adverse outcomes for both mother and infants. The authors found an attributable risk of maternal death due to breastfeeding of 69% with also an association between breastfeeding and subsequent infant death. They hypothesized that various factors such as higher viral replication during lactation and combined increased metabolic burdens of HIV-1 infection and breastfeeding could accelerate HIV-1 disease progression in postpartum mothers. However, data from a South African study \(^3\) documented no difference in mortality of HIV-1-infected women according to their children’s feeding modality (ever vs. never breast-fed). Over a mean follow-up period after delivery of 10 months, 0.49% (2 of 410) of women who ever breast-fed were known to have died compared with 1.92% (3 of 156) of women who never breast-fed. In 2005, in a meta-analysis, the Breastfeeding and HIV International Transmission Study (BHITS study) \(^4\), which used data regarding more than 4000 HIV-mothers in sub-Saharan Africa, found again no statistically significant differences in the risk of mortality during the 18-month period after delivery according to children’s feeding modality (ever vs. never breast-fed).

Othieno et al, in this recent prospective study in Kenya designed primarily to assess maternal HIV-1 disease progression, document a significantly higher rate of decline in CD4 cell count and body mass index during prolonged breast-feeding among mothers which however does not translate in a difference in HIV-1 RNA levels or mortality over the 2 year postpartum period. Importantly they noted no difference in CD4 cell count decline among HIV-infected women who weaned at 6 months and those who never breastfed. This data suggest that breastfeeding may only have a minimal adverse
effect on CD4 count during the recommended six-month period of exclusive breastfeeding recommended by WHO.

In the editorial commentary, Wilfert and Fowler ascertain that the current preponderance of evidence looking at the association of breastfeeding and maternal mortality indicates now that HIV-infected mothers are not compromised by breastfeeding their infants. New data regarding the use of highly active antiretroviral treatment (HAART) to protect both the breastfeeding mother and her HIV-exposed infant are currently being assessed and will hopefully provide information on the best strategy for reducing MTCT in order to promote maternal health and maximise HIV free infant survival.

References:
1. Wilfert C. JIDS 2007; 195; 165-167
4. BHITS. JIDS 2005; 39; 4; 430-8

Paediatric HIV care

Mortality and hospital admission rates

Note appearing in HIVCare_07_07 and commenting to the following paper:

A major article was published in the 15th of May 2007 edition of Clinical Infectious Diseases investigating the benefits of cotrimoxazole prophylaxis among HIV-infected African children. Cotrimoxazole has been shown to substantially reduce deaths non related to pneumocystis carinii pneumonia and is currently recommended for primary prophylaxis in all infants born to HIV infected mothers in industrialized and resource poor settings, starting at 6 weeks of age and continuing until the HIV negative status has been confirmed. Its use is also recommended among HIV-infected children with CD4 count lower than 15% of the total lymphocyte count.

The CHAP trial in Zambia was the first randomized placebo-controlled trial assessing the efficacy of cotrimoxazole prophylaxis in children (median age at recruitment, 4.4 years) living in areas with high levels of bacterial resistance to this antibiotic. In 2004, this trial showed a 43% reduction in mortality and a 23% reduction in hospital admissions across all ages and levels of CD4 cell percentage, as well as a 2-year cumulative probability of dying in hospital from a serious bacterial infection (predominantly pneumonia) of 7% in the cotrimoxazole group and 12% in the placebo group (P=0.08). Then Walker et al 2 analysed the determinants of survival, and described how malnutrition and hospitalizations for respiratory/bacterial infections predict mortality independently of immunosuppression, suggesting that these determinants capture HIV- and non-HIV related mortality, whereas oral candidiasis was a proxy for immunosuppression.

In this recent paper, Walker et al studied mortality and hospital admission rates during 3 periods over calendar time from March 2001 to June 2006: during the CHAP trial (comparing placebo versus cotrimoxazole prophylaxis), as well as after trial closure when all children received cotrimoxazole in a closed cohort and lastly during early and late antiretroviral therapy (ART) availability. This analysis allowed to address a major bias (e.g. confounding by indication) when directly comparing children who are initiating ART or cotrimoxazole prophylaxis with those who are not.

These results are interesting as data collected during these periods have provided original data on the natural history of HIV infection in older children and allowed comparison of various periods encompassing eras of absence of treatment, daily cotrimoxazole prophylaxis, and receipt of ART. After the trial, mortality rates decreased in the placebo group when children initiated cotrimoxazole prophylaxis until it matched rates observed in the group of children originally randomized to antibiotic prophylaxis during the trial. During the period of ART availability, mortality and hospital admission rates decreased even further by 6 and 3 fold respectively; this impact of ART being similar to what was observed in resource rich countries. This reduction in hospital admissions, as the authors point out, may result in important cost implications in the context of overburdened pediatric wards throughout sub-Saharan Africa and further cost effectiveness data are being analyzed.

The added impact of cotrimoxazole in those children on ART requires further investigation even though these data 3 might suggest that there may be a role for continuing the relatively inexpensive cotrimoxazole prophylaxis alongside antiretroviral therapy, as it is currently recommended for children.
under 5 years of age in the WHO guidelines. The authors call for the urgent need of placebo-controlled randomized trials in order to answer the important question on when antibiotic prophylaxis could be stopped in children on ART.

References
1. Chintu et al. 2004 Lancet 364;1865-71

Early mortality of HIV-infected infants

Note appearing in HIVCare_09_07 and commenting to the following paper:

Note on a ground-breaking study in which investigators at the Sidney IAS conference last July reported critical interim results from the CHER phase III randomized trial of immediate versus deferred antiretroviral therapy (ART) for 6- to 12-week-old HIV infected infants in South Africa. Though this study has not yet been published, we have chosen to highlight its importance as it may have an immediate or at least rapid impact upon paediatric treatment guidelines in resource-limited settings and is likely to affect practice as well as encourage further research. The premises for this research study were that ART in infants is known to be complex but probably worth to initiate due to the early and high risk of death and disease progression in infancy as well as the poor predictive value of CD4 count and plasma viral load as indicators of disease progression. Comparative prospective data were thus needed to inform on ART guidelines in vertically HIV-infected infants.

At present, the World Health Organization (WHO) guidelines encourage the treatment of infants <18 months when CD4 percentage is <25% or according to clinical criteria (stage III and IV). The hypothesis of this study was that early limited ART until the 1st or 2nd birthday will have a long term benefit by delaying disease progression and delay time when long-term continuous ART needs to be started.

In this randomized trial, the investigators reported that 375 infants diagnosed HIV-infected before 12 weeks, ART naïve except for prevention of mother-to-child transmission (PMTCT) and with CD4 % >25% were enrolled into three arms: 1/ the differed arm (n=125), 2/ the short-course arm to 1st birthday (n =125) and lastly a long-course arm up to the second birthday. Infants were started or restarted on ART if CD4 %< 20% (<25% from August 2006) or in case of clinical events and follow-up is scheduled for a minimum of 3.5 years. Primary endpoints were death or failure of first-line regimen, which in this trial was a regimen of zidovudine, lamivudine and ritonavir- boosted lopinavir.

An independent review panel closed the differed arm in June 07 when the risk of death proved 75% lower in the 252 early-treated children compared to the 125 children randomized to the differed arm. After a median follow-up of 32 weeks (inter-quartile range: 20-48), 10 children (4%) had died in the early-treated arm versus 20 (16%) in the late-treated arm (Hazard ratio: 0.24; [95% CI/ 0.11-0.52], p=0002).

These provocative although interim results have shown directly for the first time that early treatment in infants might be the way forward to avoid the high mortality seen in vertically HIV-infected children. A move toward earlier treatment in infants will require timely review of current international guidelines. Also as the authors point out, these results support the need for enhanced effectiveness of PMTCT programmes and the promotion of early infant diagnosis leading to effective transition to care. Finally, whether pediatric ART can be interrupted later on after such early initiation is the last scientific question the CHER trial should answer within the next two years.

References
Fixed-dose combination antiretroviral therapy

Note appearing in HIVCare_04_07 and commenting to the following paper:

We are commenting here on an article published in the December 2006 issue of AIDS where O’Brien et al provide early treatment outcomes results in children using adult fixed-dose combination (FDC) antiretroviral tablets in eight countries where Médecins sans Frontières (MSF) have provided HIV care and treatment since 2000. One of the main obstacles to treating HIV infection in children living in resource-limited settings (RLS) is the lack of practical, affordable and appropriate pediatric formulations available and the reported MSF experience provides much needed data regarding the use of alternative temporary low-cost solutions used as first line regimens in children. The main advantages of using FDC adult formulations are that they are widely available in most ART programs worldwide, easily administered in comparison to syrups, are much less costly and thus affordable for scaling up at country level and reduce the pill burden facilitating adherence and thus reducing the risk of developing subsequent viral resistance. MSF began offering ART in RLS in 2000 with more than 57000 individuals on treatment in more than 30 countries by the end of 2005. The aim of this study was to determine early outcomes and assess safety in children treated with adult generic FDC tablet Triviro containing stavudine (30 or 40mg), lamivudine 150mg and nevirapine (NVP) (200mg) administered whole, or cut in half, in children weighing more than 10kgs. O’Brien et al had previously reported good early outcomes in a retrospective study among 568 children who initiated nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based antiretroviral therapy. Indeed, after 12 months of treatment, survival probability was 0.89 (95% confidence interval, 0.86–0.92), with no significant difference among children stratified on the basis of baseline immunological levels; 62% had attained a CD4 cell percentage >25%, and 7% continued to have a CD4 cell percentage <15%. Their results were similar to those published from resource-rich settings although the children from resource-rich settings were mainly ART nonnaive, less immunosuppressed (i.e., the CD4 cell percentage was >15% for 33%–54% of the cohorts), and were treated with mainly protease inhibitor–containing regimens.

In the study O’Brien et al have published recently, a total of 2047 children, of which 1184 (60%) (median age of 7 years; IQR: 4.6-9.3), were given adult FDC antiretroviral tablets and were followed for a median of 6 months (IQR:2-12months). At 12 months they observed a median CD4 percentage gain of 15% in children aged between 18-59 months and a median CD4 gain of 275 cells/microl (IQR: 84-518) in those aged 60-156 months. Early outcomes were satisfactory with 85% of children still alive and on ART, 5% of deaths, 1% having stopped ART, 3% lost to follow up and 3% with unknown outcomes. Regarding safety, 4% of children reported side effects with only 2% having severe enough events to require change of treatment.

Limitations of this study were numerous due to operational constraints; only short follow up data was available with no data on longer term outcomes, limited information on immunological outcomes, probable under-reporting of antiretroviral adverse events due to lack of standardized reporting across sites and no measure of antiretroviral drug level to confirm therapeutic adequacy. Regarding the last point, it is particularly critical that optimal NVP plasma concentrations are achieved as NVP has a low resistance barrier and a high level of cross-resistance to other NNRTI. However reassuringly, a previously published study in Thailand using FDC adult (GPO-VIR containing stavudine, lamivudine and NVP) tablets, whole or in fractions, reported satisfactory results in terms of plasma drug levels in children. They found that out of 34 children having been given these tablets as their first line regimen, only one had minimum plasma NVP level concentrations of less than 3.4micrograms/ml which is the cut-off point concentration associated with adequate long-term virological response. It is known that pill cutting may alter absorption and cause inaccurate drug dosing however satisfactory plasma concentrations of NVP were found even though 71% of these children were receiving broken tablets as part of their standard dose. O’Brien et al conclude that although far from ideal, these preliminary results using FDC adult tablets in children are encouraging whilst ART programmes worldwide await for other affordable and more adapted pediatric formulations to become rapidly available.

References:
Eligibility model for antiretroviral treatment

Note appearing in HIVCare_11_07 and commenting to the following paper:

Notes: Little et al. present an original model to estimate the number of vertically HIV-infected children in need of antiretroviral therapy (ART) in resource-limited settings. It is of great importance to ascertain the number of children in need of treatment in such a context and particularly in sub-Saharan Africa where 90% of the paediatric infection occurs. The model considers antenatal HIV prevalence, the risk of transmission before or at birth, infant feeding policies and their associated risk of transmission, use of cotrimoxazole (CTX) to prevent opportunistic infections, use of ART and mortality rates at different ages by disease stage and according to ART regimen received. Background mortality rates are inferred from the mortality rates of non-infected children of HIV-positive mothers. Built on an Excel spreadsheet, it is easy to implement and can be used in ART programmes at national or local level. Using South Africa as an illustration, the authors provide an illustration of the model for programmatic purposes to estimate the number of HIV-infected children at different ages that would become eligible for ART. They calculated that without ART and CTX prophylaxis, with the rapid disease progression and high mortality rate early in life and the difficulty of diagnosing vertically-acquired infection in young infants, the number of infected infants surviving the first year who become eligible for treatment is relatively small. When CTX is available for all children under 18 months, and for all symptomatic children, the substantially reduced mortality results in an increased proportion of infants who develop moderate to severe disease surviving long enough to be diagnosed and become eligible for treatment. On the other hand, ART when available only to children of one year or older, only impacts on numbers of surviving children known to be infected. As children who become eligible for treatment remain on treatment for the rest of their lives and the mortality rate when on ART is dramatically reduced, there is an accumulation of children in the treatment category.

With both ART and CTX for all infants there is a rise in the number of children eligible for ART and the number of children alive and not on treatment. By the end of the first year the numbers of eligible children would approximately double than without early treatment. This then substantially increases the numbers on treatment across all age ranges. As May and Egger pointed out in a commentary in the same issue of the journal, the data feeding this illustration come from a pick-and-mix of studies, and sometimes from a different geographical area than South Africa (from Côte d'Ivoire for instance). Hopefully, with the scaling-up of ART, and the monitoring and evaluation that follows these initiatives; more data to inform such valuable models will become widely available. An interesting possible use of the model will be to evaluate the success of an intervention program either at programmatic level or at disease treatment level by predicting the number of HIV-infected children born or eligible for treatment that would be expected under the new regimen and comparing these to the actual numbers observed.

We are commenting here on an article published in the April 2007 issue of JAIDS where Jamisse et al provide data regarding toxicity associated with highly active antiretroviral therapy (HAART) among...
HIV-1 infected pregnant women treated with NVP based regimens in Mozambique. The authors found that the occurrence of hepatotoxicity was rather high with 8% of the 146 women developing more than grade II hepatotoxicity and 3% developing severe grade III/IV hepatotoxicity. They also found that there was a significantly higher rate of hepatotoxicity among women with higher CD4 counts > 250cell/microl (6% compared to 0% in women with CD4 < 250 cells/microl) suggesting that laboratory monitoring of pregnant women under NVP containing HAART might be necessary especially in those with higher CD4s.

In the light of the 2006 WHO revised guidelines for PMTCT recommending that HAART be considered for pregnant women with CD4 count <350cell/microl, this recent study is interesting in the midst of continuing debate over NVP based toxicity in pregnant women needing treatment for their own health. In the past several years, contradictory studies have been published. Hitti et al in 2004 described in the Pediatric AIDS Clinical Trial Group Protocol (PACTG) a prospective study on 38 ART naive pregnant women randomised to either NVP or Nelfinavir based HAART. They reported rather worrisome results with high incidence rates of treatment limiting hepatic or cutaneous toxicity in pregnant women with higher than 250 CD4 cells. Furthermore in South Africa, Sanne et al reported data demonstrating a high risk (17%) of early hepatotoxicity associated with the use of nevirapine mainly in African (non pregnant) women with relatively high baseline CD4+ cell counts (mean, 398 cells/mm3) and they also found an association with low body-mass index (BMI) <18.5 as an independent risk factor. All these alarming studies brought about a notification from the manufacturer Boehringer Ingelheim which declared that due to the 12 fold increased risk of severe hepatotoxicity in women with CD4 counts higher than 250 cells/microl,they issued a warning on the risk of using NVP based HAART without close monitoring in pregnant women with high CD4 cell counts. However recently in 2006, a Brazilian study on 197 pregnant women treated with NVP based HAART reported 6% of hepatotoxicity with no severe grade III/IV hepatotoxicity. Observations regarding NVP induced toxicity are important, because nevirapine is commonly used as a component of first-line therapy in resource-limited settings, especially in women. These findings need to be taken into account in future international WHO recommendations and as the authors point out, it might be important for programs in resource poor settings to consider monitoring of ALT/AST levels during the first months of therapy in order to identify early, and potentially reversible, drug-induced hepatotoxicity.

References:
2. Hitti et al. JAIDS 2004; 36:772-776

Immune reconstitution inflammatory syndrome

Note appearing in HIVCare_02_07 and commenting to the following paper:

Manosuthi et al in a retrospective study conducted in Thailand on 167 patients co-infected with HIV and TB, report on the incidence, risk factors and mortality rate of Tuberculosis Immune Reconstitution Inflammatory Syndrome (TB IRIS). The interest of this article lies in the fact that there is currently an increasing of highly active antiretroviral therapy (HAART) in resource poor countries often with a high burden of TB, associated with late presentation of patients with advanced disease, which in the lung run will result in large numbers of very immunocompromised patients receiving HAART and thus at risk of developing IRIS. However the determinants of IRIS occurrence in patients with TB remain unknown, with limited clinical data allowing creating clinical guidelines. The first reports describing TB associated IRIS were published in 1998 with frequencies varying between 29%-36% amongst the various studies however mostly retrospective in design. IRIS results from the rapid reversal in immune function with an exaggerated inflammatory immune response to an opportunistic pathogen during immune restoration. The difficulty of diagnosis results from the absence of a clear-cut definition, lack of diagnostic tools and clear guidelines for the clinical management as well as the need to exclude alternate diagnosis such as non TB related illnesses, drug toxicity or treatment failure (drug resistance, non compliance to TB treatment). Although most patients present short-lived minor
clinical problems, this syndrome can also be associated with significant morbidity and the authors point out that physicians running ART programmes worldwide need to be aware of the occurrence of the determinants of IRIS. In the largest cohort study to date, the authors describe the baseline characteristics of patients with and without IRIS. IRIS occurred in 12.6% of coinfected patients on ART and TB treatment with a median CD4 cell count of 36 (15-69) cells/mm3. There was an 8-fold higher risk of having IRIS in those with extrapulmonary TB (P<0.0001). However in this study the authors did not find that an increment of CD4 cell count was associated with IRIS as was shown in previous reports.1∧4 Other findings in previous reports1 have shown an association of IRIS with lower CD4 cell count, higher viral load (VL) before ART, greater reduction in VL6 and higher increment of CD4 cell count as well as initiation of HAART during the first 2 months of TB treatment. In an article by Lawn and al4 where 27 papers on IRIS were reviewed, median duration of TB treatment was 8 weeks (IQR: 5.5-11.5 weeks) with a nadir CD4 of 51 (IQR:26-103 cells/microl). Lawn1 also found that lymphadenopathy was the most frequent manifestation of IRIS (71%) followed by the development or deterioration of parenchymal lung disease (28%). Possible bias exist in reported cases in the literature whereby cases occurring soon after initiation of HAART are more readily attributed to IRIS than those occurring remotely.1 The authors in this paper conclude that strategies should be devised to identify patients at risk of IRIS as well as to prevent IRIS in patients about to commence antiretroviral therapy, stressing the need to carefully screen for TB before commencing HAART7∧8. This raises the important issue of the optimal timing between antiretroviral and anti tuberculosis treatments and clinical trials are needed to help physicians better understand when to initiate HAART in severely immunocompromised patients in the context of TB and adequate guidelines resulting from prospective studies are needed to identify TB IRIS risk factors9.

References

Tuberculosis incidence

Note appearing in HIVCare_10_07 and commenting to the following paper: Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Mouton LH, King BS, Efron A, Moore RD, Chaisson RE, Durovni B. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS 2007;21(11):1441-1448.

This article recently published in AIDS addresses the question of the added value of isoniazid preventive therapy (IPT) on tuberculosis (TB) incidence in an HIV-infected population with high levels of antiretroviral treatment (ART) use. As TB is among the most common causes of morbidity and mortality in people living with HIV, causing at least 12% of HIV deaths worldwide, this is an important public health issue affecting high TB and HIV-burdened resource-limited settings. The premise for this observational study was that, even though isoniazid (INH) IPT in HIV-infected patients is known to lower TB incidence by 70–90%1, the use of such prophylaxis has been tempered by long term concerns regarding the durability of protection, drug resistance, toxicity as well as...
adherence issues limiting the uptake of INH prophylaxis. In settings where the main issue is the
detection of active TB cases, implementation of IPT has thus been delayed and remains limited even
though several studies have shown that active TB can be excluded using relatively simple screening
measures. Moreover, many studies have already shown that ART is associated with reduced TB
incidence. Lawn in 2005 reported that the TB incidence density rate, which was 3.5/100 person-
years (PY) in the first year of ART significantly decreased during follow-up, reaching 1.01/100 PY in
the fifth year in South Africa (p=0.002). However, the incidence of TB remained unacceptably high
after ART was initiated and patients with advanced pre-treatment immunodeficiency still had a
persistently increased risk of TB on ART.

The authors of this study carried out in 29 HIV clinics in Rio de Janeiro, Brazil and using
retrospectively collected data, assessed the association between a history of ART or IPT, or both, and
the risk of active TB during a 2-year period. ART and IPT were treated as time-dependent exposures
and data from 11 026 HIV-infected subjects were analysed. Cumulatively, 74% of them were on ART
and IPT was received by 10%, with 834 (76.1%) individuals having completed six months of
prophylactic treatment and 17% having had a previous diagnosis of TB.

The authors found a high TB incidence in this Brazilian urban population with high levels of ART use,
with an overall incidence of 2.28 cases per 100 PY, 4.01/100 PY with neither ART nor IPT, 1.90/100
PY (95% CI 1.66–2.17) on ART alone, 1.27/100 PY (95%CI 0.41– 2.95) on IPT alone and 0.80/100
PY (95% CI 0.38–1.47) on both ART and IPT. ART in a multivariate analysis was independently
associated with a 59% reduction in TB incidence, whereas the use of both IPT and ART reduced the
risk further by 24%.

This observational survey concluded that the combined effect of IPT and ART could have a greater
impact on TB incidence than the use of ART alone and therefore implementation of a public health
policy promoting the uptake of INH prophylaxis would help lower significantly the number of cases of
TB in resource-limited settings such as this one. Even though a recent WHO policy endorsing the use
of IPT in HIV-infected patients has been promoted, uptake has been very limited so far. The low
uptake of IPT does not seem rationale in so far as INH is known to be well tolerated, inexpensive and
easy to administer in addition to lowering TB incidence and that studies have not shown an increased
risk of drug resistance. Another interesting finding of this particular study was that previous TB was a
significant risk factor for incident TB in patients with higher CD4 cell counts, which also pushes
towards the need for clear recommendations regarding secondary INH prophylaxis in such
populations.

Altogether, this study tends to show the benefits of IPT in combination with ART but the duration of the
protective effect of preventive therapy remains unclear and must be clarified in future research.

References