Non AIDS complications and treatment optimizations for HIV-1 infected Thai adult patients with and without TB or hepatitis
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Summary

In this thesis we have presented studies to guide the long term care for HIV/hepatitis and HIV/tuberculosis patients in Thailand.

In Chapter 2 we conducted a randomized clinical trial to compare the efficacy of tenofovir disoproxil fumarate (TDF)-only, TDF/3TC (lamivudine) and 3TC-only as part of a cART regimen among 36 ARV naïve, chronic HIV/HBV co-infected individuals in Thailand with high HBV DNA of >100,000 copies/ml. We found that at week 48: 46% for 3TC, 75% for TDF, 64% for TDF/3TC had HBV DNA suppression <170 copies/ml. Furthermore, HBV resistance was detected only in the 3TC group (2 subjects). HBeAg loss and HBsAg loss were observed in 33% and 8% in this cohort, respectively. We concluded that combination therapy with TDF and 3TC is to be preferred over 3TC-only based cART for HIV/HBV co-infected individuals.

In Chapter 3 we performed a randomized clinical trial to compare the efficacy of TDF/FTC (emtricitabine) versus FTC alone as part of cART among 16 ARV naïve, chronic HIV/HBV co-infected individuals with high HBV DNA of >100,000 copies/ml. We found that at week 48, the proportion of patients with HBV DNA suppression <170 copies/ml was significantly higher in the TDF/FTC treated group (90%) than in the FTC treated group (33%). It is plausible that FTC enhances the potency of TDF when the drugs are concomitantly used. We concluded that combination therapy with TDF and FTC is to be preferred over FTC-only based cART for HIV/HBV co-infected individuals.

In Chapter 4, the incidence, characteristics, predictors and subsequent outcomes of hepatic flare occurring during the first 12 weeks after cART initiation (early hepatic flare) were reported among 36 advanced HIV/HBV co-infected subjects with a median CD4 cell counts of 36 cells/mm³. Early hepatic flare (ALT ≥grade3) occurred in 22% at a median of 56 days after cART. The high incidence of hepatic flare and the particularly high rate of HBeAg seroconversion among HBeAg-positive early hepatic flare cases suggest a close relationship between immune reconstitution, hepatic inflammation and HBeAg seroconversion.

In Chapter 5, liver biopsies of 16 HIV/HBV co-infected patients and 16 HBV mono-infected patients were examined by immunohistochemical staining for markers of T-cell and monocyte infiltration and activation, natural killer cells, hepatic stellate cell activation and apoptosis. We found that intra-hepatic apoptosis was increased in advanced HIV/HBV co-infection compared to HBV mono-infection. We concluded that the increase in intra-hepatic apoptosis could potentially contribute to the accelerated liver fibrosis seen in the setting of advanced HIV/HBV co-infection.

In Chapter 6, serum levels of 25(OH)D prior to and after TDF therapy in 158 HIV/HBV co-infected Thais were examined. We found high prevalence of hypovitaminosis D [25(OH)D < 30 ng/ml] at 72.2% prior to TDF and 84.2% after TDF. Vitamin D levels declined after a median of 5 years of TDF treatment. Female gender and prolonged ART > 5 years were independently associated with hypovitaminosis D. Given that HIV/HBV co-infection requires long term HBV-active drugs, including TDF which can contribute to bone loss, routine vitamin D assessment and supplementation should be considered.
In Chapter 7, liver fibrosis among HCV patients with and without HIV infection was assessed by transient elastography (TE). We found HCV genotype 3 was the most prevalent (49.5%), followed by genotype 1 (32%) and 6 (13%) in HIV/HCV co-infection. Similarly, genotype 3, 1 and 6 were detected in 46%, 35% and 18%, respectively in HCV mono-infection. For IL28B, 91% were major allele (CC) for rs12979860. Almost 70% of the HIV/HCV co-infected patients had significant liver fibrosis (TE >7.1kPa) and 41.6% had advanced liver fibrosis (24% cirrhosis). In addition, patients with hypovitaminosis D (25(OH) D levels < 30 ng/ml) were almost three times more likely to have advanced liver fibrosis. The findings of high prevalence of advanced liver fibrosis (41.6%) in this study highlight the urgent need for HCV treatment and HCC screening for patients in resource-limited settings. Given that 47% of the HCV patients in our studies have HCV genotype 3 and 90% of them have IL-28 B rs12979860 CC allele, they are good candidates for HCV treatment with pegylated interferon alfa and ribavirin.

Chapter 8 provides an overview of the challenges in providing treatment and care for viral hepatitis among individuals co-infected with HIV in resource-limited Settings

Chapter 9 provides an overview of HIV associated tuberculosis. Drug interactions between rifampicin or rifabutin and NNRTI (efavirenz: EFV, nevirapine: NVP) and boosted PIs are reviewed.

In Chapter 10 we performed randomized control trial to investigate the optimal dose of nevirapine in rifampicin treated patients. We found that a higher dose of nevirapine (600 mg per day) was associated with a higher rate of nevirapine hypersensitivity compared to the standard dose (400 mg per day). We concluded that standard dose of nevirapine could be safety used as an alternative option in cases with efavirenz toxicity.

In chapter11, the strategy of using a modified dose of boosted IDV/r at 600/100 mg twice daily and rifampicin in HIV/TB co-infected Thai patients was examined. We found that IDV/r 600/100mg twice daily had subtherapeutic IDV concentrations when it was being used with rifampicin. However, the majority of patients achieved plasma HIV-1 RNA levels below the limit of detection at 48 weeks. The safety and efficacy of rifabutin with boosted PI should be further explored in HIV/TB co-infected patients.

In Chapter 12, the feasibility and the effect of TST and IPT on the incidence of TB in the cART era was assessed in 4339 subjects at the Thai Red Cross AIDS Research Centre. We demonstrated that TST and IPT were feasible in a setting of adequate man power (nurse care management) and integration of HIV services along with TST and IPT. None of the IPT cases had active TB during 3 years of follow-up. We concluded that HIV-infected patients with CD4 cell counts < 200 cells/mm³ and positive TST, IPT plus cART should be performed.