Non AIDS complications and treatment optimizations for HIV-1 infected Thai adult patients with and without TB or hepatitis
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CHAPTER 13

General discussion
Introduction

Hepatitis B virus (HBV) and tuberculosis (TB) are well known contributors to morbidity and mortality among human immunodeficiency virus (HIV)-infected individuals worldwide. Co-infection with HIV and HBV or TB is a growing public health concern, especially in resource limited settings where these infections are highly prevalent. Early in the HIV/AIDS epidemic most HIV infected patients were expected to die from HIV/AIDS, and less attention was devoted to other long-term conditions, liver disease in particular. Since the widespread availability of combination antiretroviral therapy (cART), there has been a dramatic decline in HIV/AIDS-related morbidity and mortality as well as a significant increase in the life expectancies of HIV-infected patients worldwide [1]. However, the improved survival after effective cART has been associated with higher mortality and morbidity rates contributable to chronic infection with HBV and hepatitis C virus (HCV) [2-4].

HBV and HCV are viral infections of the liver. They can lead to serious consequences including liver cirrhosis, end stage liver disease and liver cancer. Most studies show that HIV infection leads to more aggressive hepatitis B and C liver diseases, including higher risk of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC)[5-11]. However, the effect of HBV and HCV on HIV disease progression is less clear. Most studies show that HBV and HCV do not accelerate HIV disease progression, but these infections may impair immune system recovery after cART. Furthermore, HBV and HCV co-infections can complicate treatment because they put the patients at risk for developing cART-associated hepatotoxicity [12], especially those with advanced liver damage.

The prevalence of HBV in HIV infected Thai patients is 8-10% and it is 7.8-8.7% for HCV [13, 14]. Because HBV and HCV genotype distribution in Thailand differs from that in the West, little is known regarding the pathogenesis and treatment outcomes of HBV and HCV co-infections in Thais. In addition data on appropriate HIV treatment in HIV/TB co-infected patients who could not use first-line efavirenz-based regimen were lacking. Therefore, this thesis focuses on studies that inform the optimization of cART for HIV/HBV, HIV/HCV and HIV/TB co-infected patients. The HBV and HCV related studies were conducted at two clinics in Bangkok: the HIV Netherlands Australia Research collaboration (HIV/NAT) /Thai Red Cross AIDS Research Centre and the King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University. The TB studies were performed at 4 sites in Thailand: HIV/NAT, Bamrasnaradura Infectious Diseases Institute, Chiangrai Prachanukroh Hospital, and Central Chest Institute.

Optimizing antiretroviral therapy for, and pathogenesis of liver disease progression in HIV/HBV co-infection in Thailand

The long-term goals for patients with HBV and HIV co-infection are the same as in HBV mono-infection, including delaying development of end-stage liver disease, reducing risk of liver cancer and improving survival. Currently, five nucleos(t)ide analogues (NRTIs) are approved for the treatment of chronic HBV infection. They are lamivudine (3TC), adefovir dipivoxil, telbivudine, entecavir (ETV) and tenofovir disoproxil fumarate (TDF). ETV and TDF are recommended as first-line treatment options for chronic HBV infection in HIV-uninfected population [15, 16]. Emtricitabine (FTC) also has activity against HBV but it has not yet been registered for the treatment of HBV. Treatment of both HIV and HBV are usually initiated simultaneously and treatment is generally life-long. In HIV/HBV co-infected individuals , when HIV treatment is required, two HBV-active agents: TDF combined with FTC or 3TC plus a third agent active against HIV are indicated, regardless of the HBV DNA levels or liver fibrosis stage[16-18]. TDF was available in Thailand in late 2007, and Thailand adopted its use in the guideline for the treatment of HIV/HBV co-infection in 2010 [19].

TDF, an adenosine nucleotide analogue, is highly potent against both HIV and HBV and has a high genetic barrier for HBV resistance. 3TC, an L-nucleoside analogue, is highly potent against HBV but has
a low genetic barrier [20]. Resistance rate to 3TC in HIV/HBV co-infection appears to be somewhat higher than that in HBV mono-infection: 50% after two years and 90% after four years in HIV/HBV co-infected patients [21], compared to 46% and 71% for HBV mono-infected patients [22-24]. A study in 84 HIV/HBV co-infected Thai patients found that 19 (23%) had HBV drug resistance to 3TC, and the risk factors for resistance were positive HBeAg and prolonged used of 3TC [25].

Prior to August 2008, TDF was not approved for HBV treatment in Thailand and almost all HIV/HBV co-infected patients were receiving 3TC as a single HBV drug along with 2 other agents with activity against HIV. In addition, data on efficacy of TDF in co-infected individuals were limited [26]. Therefore, in chapter 2, we conducted a randomized clinical trial to compare the efficacy of TDF-only, TDF/3TC and 3TC-only as part of a cART regimen among 36 ARV naive, chronic HIV/HBV co-infected individuals in Thailand. All patients had high baseline HBV DNA of > 100,000 copies/ml (median of 8.4 log_{10} copies/ml). HBeAg-positivity was found in 61%, and 81% had HBV genotype C. In addition, they had advanced HIV disease with a median baseline CD4 cell count of 36 cells/mm^3 and a median baseline plasma HIV-1 RNA of 4.7 log_{10} copies/ml. The study found that at week 48, the median HBV DNA reduction was not statistically different among TDF-only (4.57 log_{10} copies/ml), TDF/3TC (4.73 log_{10} copies/ml) or 3TC only (4.07 log_{10} copies/ml) (p=0.70) treatment groups. Although the viral dynamics of HBV DNA in this population were similar following 3TC-only, TDF-only and TDF/3TC based cART had advanced HIV disease with a median baseline CD4 cell count of 36 cells/mm^3 and a median baseline plasma HIV-1 RNA of 4.9 log_{10} copies/ml). HBeAg-positivity was found in 61%, and 81% had HBV genotype C. In addition, they had advanced HIV disease with a median baseline CD4 cell count of 36 cells/mm^3 and a median baseline plasma HIV-1 RNA of 4.7 log_{10} copies/ml. The study found that at week 48, the median HBV DNA reduction was not statistically different among TDF-only (4.57 log_{10} copies/ml), TDF/3TC (4.73 log_{10} copies/ml) or 3TC only (4.07 log_{10} copies/ml) (p=0.70) treatment groups. Although the viral dynamics of HBV DNA in this population were similar following 3TC-only, TDF-only and TDF/3TC based cART [27], 3TC-only therapy resulted in a lesser proportion of patients with HBV DNA suppression <170 copies/ml at week 48: 46% for 3TC, 75% for TDF, 64% for TDF/3TC. 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. The study concludes that combination therapy with TDF and 3TC is to be preferred over 3TC-only based cART for HIV/HBV co-infected individuals. Therefore, all HIV/HBV infected patients with 3TC alone had TDF added to their therapy after the study ended. Unfortunately, 1 cirrhotic patient from the 3TC-only group developed HCC 6 months later. Our study provides a strong rationale for the guidelines to recommend TDF with 3TC or FTC as dual HBV agents in the treatment of HIV/HBV co-infection [17, 18]. FTC is structurally similar to 3TC, but has a longer half-life [28], and is less likely to select for a YMDD mutation compared to 3TC [29]. Although FTC is currently not approved for the treatment of HBV, it induces a rapid and sharp reduction in HBV DNA [29]. There were also limited data from randomized studies on the efficacy of FTC or TDF/FTC in ARV-naive HIV/HBV co-infected patients. Thus, in chapter 3, a randomized clinical trial was conducted to compare the efficacy of TDF/FTC versus FTC alone as part of cART among 16 ARV naïve, chronic HIV/HBV co-infected individuals. The subjects enrolled in this study were similar to those in the study described in Chapter 2, with all having high baseline HBV DNA>100,000 copies/ml (median of 8.76 log_{10} copies/ml) and 69% having positive HBeAg. In addition, the patients had advanced HIV disease with a median baseline CD4 count of 64 cells/mm^3 and a median baseline plasma HIV-1 RNA of 4.9 log_{10} copies/ml. At week 48, the median HBV DNA reduction was statistically greater among TDF/FTC (5.32 log_{10} copies/ml) than FTC mono (3.25 log_{10} copies/ml) (p=0.03)-treated patients. Furthermore, the proportion of patients with HBV DNA suppression <170 copies/ml at week 48 was significantly higher in the TDF/FTC treated group (90%) than in the FTC treated group (33%). However, all 5 patients who had detectable HBV DNA had no mutation detected in the HBV polymerase and all had plasma HIV-1 RNA < 50 copies/ml. The excellent efficacy of TDF/FTC in this study [90% in the TDF/FTC treated group had undetectable HBV DNA at week 48 compared to 64% in the TDF/3TC treated group in chapter 2] is supported by in vitro data (using a hepatoma cell line chronically infected with HBV: AD38 cell line), showing a greater reduction in HBV DNA following treatment with TDF/FTC compared to TDF/3TC [30]. It is plausible that FTC enhances the potency of TDF when the drugs are concomitantly used [30]. In vitro studies found that FTC had a synergistic effect with TDF in treating HBV [30, 31] or HIV [32]. Thereafter, several cohort studies reported the excellent long term efficacy of TDF and FTC in HIV/HBV co-infected populations, including both 3TC naïve patients and those on 3TC experience for up to 5 years [33-35].
Because of the excellent efficacy and safety profile, and a high genetic barrier to resistance for both HIV and HBV, current treatment guidelines recommend the use of TDF in combination with either FTC or 3TC as part of a cART regimen for HIV/HBV co-infection [16-18]. At present time, TDF resistance to HBV is extremely rare [36].

With the two studies in chapters 2 and 3 showing high rates of HBeAg seroconversion (33-36%) in patients with advanced HIV/HBV co-infection, it is plausible that robust immune reconstitution following cART results in similar HBV-specific immunological control as seen after interferon-based therapy for HBV mono-infection.

Individuals with HIV and HBV co-infection are at high risk for the development of significant liver disease and guidelines recommend early consideration of HBV- cART in HIV co-infected individuals [17, 18]. Initiation of effective HIV and HBV-active therapy to co-infected individuals not only results in HIV RNA suppression and T cell restoration, but also reduces HBV DNA replication [37-39], limits further liver disease progression [40, 41], and in some cases reverses the abnormalities of end stage liver disease [42]. However, cART initiation also has the potential to cause morbidity.

Hepatotoxicity after cART initiation has been reported to occur in 2 to 14% of HIV-infected individuals [12, 43-45], and the risk increases significantly in HBV or HCV co-infected individuals [12, 43]. Definitions of hepatotoxicity vary. The most commonly used definition is the AIDS Clinical Trial Group (ACTG) one, in which an increase in ALT and/or AST above 5 times the upper limit of normal (ULN) is defined as severe hepatotoxicity (Grade 3). This criterion can also be used to define ‘hepatic flare’. The mechanisms for hepatic flare after cART initiation are multifactorial, particularly in viral hepatitis co-infected subjects, and include ARV-related toxicity, immune reconstitution, other medications the patient is taking, and other hepatotoxic agents such as alcohol. Hepatic flare appears to be particularly common within the first 3 months after cART initiation, suggesting a potential immunological component to its development. In this setting the outcome following hepatic flare may be beneficial with subsequent HBsAg seroconversion; on the other hand hepatic flare may also be associated with morbidity, and even mortality. Hepatic flare was observed in 25% of patients in the study described in Chapter 2 and in 19% in the study in Chapter 3.

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 (from the study in chapter 2) with a median CD4 cell counts of 36 cells/mm³. Eight of those subjects (22%) developed an early hepatic flare at a median of 56 days after cART with a median peak ALT of 395 U/L (range 178-2560 U/L). The majority was asymptomatic and the transaminitis resolved spontaneously with continuation of cART. However, 2 cases (25%) were symptomatic and 1 died from rapid hepatic decompensation. At week 48, all of the 5 early hepatic flare cases were still in follow-up and had ALT < 2 X ULN and undetectable HBV DNA (<170 copies/ml). The predictors of early hepatic flare were high baseline ALT and HBV DNA, and subsequent HBeAg and HBsAg seroconversion. HBeAg loss occurred in 75% of cases with hepatic flare versus 22% without early hepatic flare, and these numbers were 25% and 4% respectively for HBsAg loss.

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. The early onset of hepatic flare is potentially consistent with dysregulated immune restoration of HBV-specific responses driving hepatic inflammation control of both HBV DNA and HIV RNA following cART. This study concluded that the rate of hepatic flare was high during the first 12 weeks of HBV-active cART initiation in an advanced immunodeficient Asian population. Hepatic flare events are associated with a high rate of HBeAg seroconversion.
These findings suggest that HIV/HBV co-infected subjects initiating cART should be closely monitored for hepatic flare during the initial 3 months of therapy, particularly when both baseline ALT and HBV DNA levels are high. Since the outcome of hepatic flare may be beneficial, it is unnecessary to discontinue cART in most cases. All asymptomatic cases in our study were able to continue cART with subsequent ALT normalisation and a high rate of HBe Ag seroconversion. Symptomatic or grade 4 elevation of ALT, however, may be life threatening, especially in the presence of advanced liver fibrosis or cirrhosis and should indicate a need to hold or cease therapy. If possible, assessment of the degree of underlying liver disease should be performed in such patients, as severe underlying liver damage predicts severe hepatic flare. In such patients at high risk for adverse outcomes or in selected patients unable to tolerate cART without liver enzyme elevation, there are no data to guide how to proceed safely. A strategy of short-course lead-in anti-HBV therapy (using drugs without anti-HIV activity) could be studied as a potential mechanism to decrease HBV burden and prevent hepatic flare after cART initiation in such individuals.

The pathogenesis of accelerated liver fibrosis in HIV/HBV co-infection remains poorly understood and multiple factors may be in play. In fact, HIV infects several liver cells including Kupffer cells, portal mononuclear inflammatory cells, hepatocytes and endothelial cells[46]. Accelerated liver fibrosis in HIV/HBV co-infection may be due to: 1) Unique HBV mutations[47], 2) Reduced HBV-specific CD4+ and CD8+ T-cell responses, 3) HIV-infected hepatic stellate cells, and 4) depletion of gut CD4 T-cells.

Revill PA et al. described a novel deletion (-1G mutation) in the HBV precore/core genes and found it to be more common among HIV/HBV co-infection than mono HBV infection. This unique HBV mutations have been associated with more aggressive liver disease in HBV mono-infection, therefore, this novel deletion mutant may contribute to accelerate liver fibrosis in HIV/HBV co-infected individuals [47], however this was not the case for Thai patients. According to Tangkijvanich P et al, they did not see any major differences in the frequencies of common HBV mutations among HIV/HBV co-infected and HBV mono-infected Thai patients. Thus, HBV mutations may not contribute to disease pathogenesis in Thai patients with HIV/HBV co-infection [48].

HBV-specific CD8 +cytotoxic T-lymphocyte (CTLs) and CD4+ T- cells play a key role in the control of HBV replication and in the pathogenesis of liver disease. Both CTLs and HBV specific CD4+T-cells responses are significantly impaired in the setting of HIV co-infection [49, 50] and they are increased after treatment with cART [51]. It is possible that HIV modulation of the HBV-specific T-cells responses may alter the hepatic cytokines and subsequently high HBV DNA, chronic HBV infection [49] and liver damage [52].

Hepatic stellate cells (HSCs) are major effector cells producing fibrosis. HSCs could be activated by HIV and HBV co-infection, resulting in collagen deposition and hepatic fibrosis[53].

Lastly, it is possible that immune activation in HIV/HBV co-infection might be increased by the synergistic effect of both viruses[54] and severe depletion of gut CD4 T cells from HIV co-infection resulting in microbial translocation as measured by circulating lipopolysaccharide (LPS) [52]. LPS can directly activate cells in the liver, responsible for fibrogenesis, and have been associated with cirrhosis in HIV/HCV co-infection [55]. Crane M et al reported that LPS and soluble CD14 were significantly elevated in Thai HIV/HBV co-infection (n=55) compared with uninfected control and these levels return to normal following HBV-active cART. However, no significant association between LPS and liver fibrosis was observed[56]. It is unclear if LPS plays a role for liver fibrosis progression.

Our group have previously shown that the HBV-specific T-cell response is impaired in advanced HIV/HBV co-infection from Thailand [50], and that there is no sustained change in the HBV-specific CD8+T cells response following HBV-active cART [57].
In order to better understand the pathogenesis that drives aggressive liver disease in HIV/HBV co-infection, 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. An increase in intrahepatic apoptosis but fewer intrahepatic T cells, Kupffer cells and natural killer cells were observed in advanced HIV/HBV co-infection compared to HBV mono-infection. This finding of increased intrahepatic apoptosis is consistent with other studies in HIV and HCV co-infected patients with low CD4 cell counts [58]. The increase in intra-hepatic apoptosis could potentially contribute to the accelerated liver fibrosis seen in the setting of advanced HIV/HBV co-infection.

Vitamin D plays a major role in the calcium homeostasis and bone health. Beside its effect on bone metabolism, vitamin D is now widely recognized as a critical factor involved in the immune system, inflammatory response, and fibrogenesis [59]. These extra-skeletal actions of vitamin D are associated with the presence of a vitamin D receptor (VDR) on several cells including macrophages, natural killer cells, T and B cells. In addition, vitamin D regulates more than 200 genes that are related to immune response, cellular proliferation and differentiation, apoptosis and angiogenesis [60]. It is thought that optimal calcium absorption is correlated with a serum vitamin D level of 30 ng/ml or higher. Lower levels result in an increased production of parathyroid hormone [59, 61]. However, the optimal vitamin D level for non-skeletal activity is not fully understood. Vitamin D from the skin and diet is first hydroxylated in the liver into 25-hydroxyvitamin D[25(OH)D] which is transported to the kidney and undergoes a second hydroxylation to 1,25(OH)D in the proximal renal tubule [59]. Therefore, any disease in the liver and proximal renal tubule would interfere with production of the active metabolites of vitamin D, resulting in hypovitaminosis D (serum 25(OH)D of <30 ng/mL) and abnormal calcium and bone metabolism. Recent studies found that low serum levels of 25(OH)D correlated with severe liver fibrosis in both HCV genotype 1 mono-infected [62] and in HIV/HCV co-infected patients [63].

Hypovitaminosis D has been reported in up to 80% of HIV-infected adults from both high latitude- [64-67] and tropical countries [68, 69]. About 68%-92% of patients with chronic liver disease (mainly due to alcohol and chronic hepatitis C) have hypovitaminosis D [70]. Little is known about hypovitaminosis D in patients infected with chronic hepatitis B, with or without HIV co-infection, and hepatitis C in Asia. In chapter 6, serum levels of 25(OH)D prior to and after TDF therapy in HIV/HBV co-infected Thais were examined. Liver fibrosis was also assessed using transient elastography. Almost 90% of patients with HIV/HBV co-infection did not have significant liver fibrosis, in part due to the early initiation and prolonged treatment of HIV and HBV. Although the HIV/HBV co-infected Thai patients live in the tropics where there is sun exposure all year round, a high prevalence of hypovitaminosis D was observed: 72.2% prior to TDF and 84.2% after TDF. Interestingly, 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. However, the association of vitamin D levels and significant liver fibrosis was not observed, possibly in part due to the low prevalence of significant liver fibrosis in the study population. 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.

Liver disease progression in HIV/HCV co-infection in Thailand

A single nucleotide polymorphism near the interleukin-28B (IL28B) gene on chromosome 19, which encodes type III interferon-λ (at position rs12979860 and rs 8099917) has shown to be a prognostic indicator of HCV treatment response [71-77]. Liver fibrosis, HCV genotypes, IL28B polymorphism, pretreatment HCV RNA, and decrease in HCV viral load at 4 weeks after HCV therapy play critical roles in optimizing HCV treatment. However, most of this data arise from Caucasian populations, who are predominately infected with HCV genotype 1. In Thai HCV mono-infected patients, about 50-60% are infected with genotype 3, followed by genotype 1(30%) and genotype 6 (6-10%) [78-82].
Since the treatment of HCV is costly and has a high toxicity rate, liver fibrosis staging, HCV genotypes, pre-treatment HCV RNA, and IL28B are beneficial to identify potential non-responders before starting pegylated interferon ( Peg IFN) /ribavirin ( RBV) therapy. In chapter 7, liver fibrosis among HCV patients with and without HIV infection was assessed by transient elastography (TE). HCV genotype, IL28B polymorphism, HCV RNA and vitamin D levels were also determined. Among HIV/HCV co-infections, HCV genotype 3 was the most prevalent (49.5%), followed by genotype 1 (32%) and 6 (13%). Similarly, genotype 3, 1 and 6 were detected in 46%, 35% and 18%, respectively in HCV mono-infection. For IL28B, 91% were major allele ( TT) for rs 8099917 and 87% were major allele ( CC) for rs 12979860. In this study, patients co-infected with HCV and HIV had a higher prevalence of significant liver fibrosis: HIV-co-infected patients were 2.67 times more likely to have advanced liver fibrosis (TE>9.5 kPa) compared to HCV mono-infected patients. Almost 70% of the HIV/HCV co-infected patients had significant liver fibrosis (TE >7.1 kPa) 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. Low serum 25(OH) D levels have also been reported in patients with chronic HCV genotype 1 and were found to be associated with severe liver fibrosis [62, 63].

HCV infection, the presence of cirrhosis is the main factor for the development of HCC which occurs in between 1%-4% annually once cirrhosis is established. Importantly, the risk of HCC in HCV related cirrhosis persists in the absent of plasma HCV RNA after successful HCV treatment [83]. Since 24% of our study patients had cirrhosis. They are at high risk for developing HCC. 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.

Antiretroviral therapy in HIV/TB co-infected patients receiving rifampicin

At present, co-infection with TB and HIV is common, particularly in developing countries where both diseases are epidemic. Management of both TB and HIV has become a major public health problem and will continue to be so as access to cART expands. In the future if we start ART early, so then we will have less TB cases. Although efavirenz + 2 NRTIs is often selected as first-line antiretroviral regimen for the treatment of HIV/TB co-infection, there is nevertheless a need for alternative cART regimens in case of efavirenz toxicity or NNRTI resistance. In these cases, a ritonavir-boosted protease inhibitor (boosted PI) is often used.

In Thailand, up to 30% of HIV-infected patients have active TB [84] and 16% of active TB cases also have HIV infection [85]. Despite the availability of effective therapy for both diseases, simultaneous treatment continues to be a complex scenario due to drug-drug interactions, high pill burden, immune recovery syndrome and overlapping toxicities [86, 87]. Based on the SAPIT trial [88], initiating cART during TB treatment reduces all-cause mortality by 56% in sputum smear-positive HIV/TB co-infected patients with CD4 < 500 cells/mm³. With the completion of 3 large randomized clinical trials in 2011: SAPIT [88, 89], CAMELIA [90], and STRIDE [91], the question on the optimal time to initiate cART during TB treatment has been addressed. The results of these 3 trials show that in HIV infected patients with active TB and CD4 cell counts of < 50 cells/mm³, early initiation of cART within 2 weeks of TB treatment can reduce mortality and AIDS progression. However, early cART was associated with immune reconstitute syndrome (IRIS), but the IRIS was infrequently associated with mortality [89-91]. Therefore, the guidelines recommend that cART should be initiated within 2 weeks of TB treatment in HIV/TB co-infected individuals with CD4 cell count of < 50 cells/mm³ and it can be delayed to 8-12 weeks of TB treatment in cases with CD4 count >50 cells/mm³ [17, 18].

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Rifampicin is a crucial component of effective anti-TB treatment because it is more effective than non-rifampicin containing regimens and allows for a shorter course of TB therapy with high rates of treatment success[92-94]. Unfortunately, rifampicin is a potent inducer of hepatic cytochrome P450 3A (CYP3A) and drug transporter P-glycoprotein [95], which results in markedly lower plasma concentrations of NNRTIs and boosted PIs. Drug interactions between rifampicin or rifabutin and NNRTI (efavirenz: EFV, nevirapine: NVP) and boosted PIs are reviewed in chapter 9.

Although an efavirenz based regimen is preferred for first-line cART in HIV infected patients with active TB, in case of EFV toxicity or intolerance nevirapine could be an alternative option. In Thailand, generic nevirapine fixed dose combinations are the least expensive and most commonly used first-line therapy. In chapter 10, the optimal dose of nevirapine when it is being used with rifampicin in HIV/TB co-infected patients was investigated. The study 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). Although nevirapine concentrations are reduced by approximately 20-55% with concomitant rifampicin use, with standard dose therapy they generally exceed the concentration necessary to suppress HIV in vitro [96, 97]. Several studies from Monosuthi W et al from Bamrasnaradura Infectious Diseases Institute in Thailand showed excellent virological, immunological and clinical outcomes of standard dose of nevirapine- compared to efavirenz-based regimens [98-102]. In addition, studies from Malawi [103] and Botsawana[104] also showed good efficacy of standard dose of nevirapine treatment in HIV/TB co-infected patients receiving rifampicin. However, our findings are inconsistent with study results from India [105] and South Africa [106] where it was found that nevirapine was inferior to efavirenz when used with rifampicin. High nevirapine plasma concentrations in HIV-infected Thais [97, 107] may explain the adequate drug levels when standard dose nevirapine was used, whereas in South Africa, a high proportion of patients had sub-therapeutic levels of nevirapine and subsequently inferior clinical outcomes [108].

Although HIV/TB co-infected patients with efavirenz toxicity could benefit from using raltegravir 800 mg twice daily with rifampicin [109, 110], this strategy may not be applicable for resource-limited settings due to the high cost of raltegravir. Therefore, Thai guidelines recommend to use nevirapine as an alternative option in cases with efavirenz toxicity[19].

Since 2008, the Thai Ministry of Public Health (MOPH) has massively scaled up its ART treatment programs under the Thai Universal Health coverage system managed by the National Health Security Office (NHSO). Up to 95% of HIV infected patients use a NNRTI first line regimen, and 10% develop NNRTI failure each year (Unpublished data from NHSO). TB may develop during NNRTI failure or while patients are receiving a boosted PI as a second-line regimen. Unfortunately, rifampicin markedly lower plasma concentrations of boosted PIs[95]. Several studies in healthy volunteers have attempted to overcome this by using higher doses of boosted PIs, however, high rates of liver toxicity were seen [111, 112]. WHO and DHHS guidelines [17, 113] therefore recommend to refrain from using a boosted PI with rifampicin until more data are available. These guidelines instead recommend rifabutin, a weak inducer of CYP3A that appears to cause less pronounced reductions in boosted PI plasma concentrations than rifampicin [7]. Although rifabutin has recently been added to the WHO Essential Medicines List, it is not yet available in Thailand and in many other countries. In addition, data supporting rifabutin efficacy and safety in HIV-infected patients are scarce [114] and when used with a boosted PI, dose adjustment of both drugs is required [115]. In Thailand, indinavir/ritonavir ((IDV/r)-based cART was the most used boosted PI regimen for the national program until lopinavir/ritonavir (LPV/r) became more widely available in 2008. Although IDV is no longer the preferred option, it is still used in a minority of patients. In chapter11, the strategy of using a modified dose of boosted IDV/r and rifampicin in HIV/TB co-infected Thai patients was examined. Boosted IDV was selected because it was the most used protease inhibitor in Thailand at the time this study was conducted. In addition, the pharmacokinetics, efficacy and safety data of IDV/r were well documented in Thais [116-123].

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This study showed subtherapeutic concentrations of IDV in Thais who used IDV/r 600/100mg twice daily with rifampicin 600mg once daily. However, the majority of patients achieved plasma HIV-1 RNA levels below the limit of detection at 48 weeks. This finding is consistent with other studies using IDV/r [124], atazanavir/r [125-127], saquinavir/r [128, 129], and LPV/r [130], which showed a reduction of PI concentrations when used with rifampicin despite increasing the doses of the PI and/or low dose ritonavir. The safety and efficacy of rifabutin with boosted PI should be further explored in HIV/TB co-infected patients.

Latent TB infection is defined by having a positive tuberculin skin test (TST) without clinical symptoms of TB [131]. The prevalence of latent TB in Southeast Asia is around 46%, which is much higher than in Europe (14%) and the USA (15%) [132]. Although the efficacy of isoniazid (INH) prophylaxis (IPT) has been established in several studies from Haiti [133-135], Uganda [136], Kenya [137, 138], Zambia [138] and the USA [139], IPT has not been implemented in Thailand. In Chapter 12, the feasibility and the effect of TST and IPT on the incidence of TB in the cART era was assessed at the Thai Red Cross AIDS Research Centre. With the large sample size of 4339 subjects, this study 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. The study also showed high efficacy of IPT with none of the IPT cases developing active TB during 3 years of follow-up. Another study from Thailand [140] confirmed the efficacy of IPT in advanced HIV-infected patients with positive TST: in HIV-infected patients with CD4 cell counts < 200 cells/mm³, IPT plus cART was beneficial in reducing active TB during the first 6 months of cART. Thus, the strategy of using IPT in advanced HIV-infected patients with positive TST is endorsed by WHO[141].

Conclusions and future perspectives

HBV, HCV and TB infections represent a major public health dilemma causing an additional burden on the health care system beside that of HIV treatment and care, especially in resource-limited settings. The introduction of cART in this region has substantially improved the life expectancy for millions of people living with HIV/AIDS. Chronic liver diseases are becoming a leading cause of morbidity and mortality and will be increasingly frequent as patients live longer. Over the past decade, cutting edge research has led to the improvement in the management of chronic HBV, chronic HCV and TB in HIV-co-infected patients. However, chronic hepatitis B and chronic hepatitis C diseases remain a major silent killer in HIV infected individuals, which is due in part to the under recognition of these diseases. Thailand is a high endemic area for HBV infection, however, only 58%-69% of HIV infected patients have been screened for HBV infection [142, 143] and only 36.3% had HBV screening prior ART.

This thesis has shown that TDF plus FTC [144] or 3TC [145] in cART is highly effective against HBV in the HIV-infected population. Our findings strongly confirm the current treatment guidelines, which recommend 1) the use of TDF in combination with either FTC or 3TC in cART regimens for HIV/HBV co-infected patients, and 2) early initiation of HIV treatment in this population [16-18]. Given the high rate of hepatic flare during the first 12 weeks of cART, liver enzymes should be closely monitored during this period, particularly when ALT and HBV DNA levels are high. Although the majority of hepatic flare cases is benign in which cART can be continued, life threatening complications may occur, especially in patients with advanced liver fibrosis or cirrhosis. In such cases cART should be temporary stopped. In order to reduce the risk of early hepatic flare in patients with advanced HIV infection or chronic active hepatitis B, a strategy of short-course lead-in anti-HBV therapy (using drugs without anti-HIV activity) could be studied as a potential mechanism to decrease HBV burden and prevent fatal hepatic flare after cART initiation. In the presence of HIV, HBV-related liver disease progression is accelerated and liver-related mortality is significantly increased. The mechanism of how HIV infection accelerates the progression of HBV-related liver disease is poorly understood and multiple factors may contribute. We have recently shown [146] that increased intra-hepatic apoptosis could contribute to accelerated liver fibrosis in the setting of advanced HIV/HBV co-infection. Although evidence is scarce, alteration of the
HBV life cycle after multiple cells in the liver have been infected with HIV, might be another potential cause of liver fibrosis [46]. Furthermore, an impaired HBV-specific T-cell response in advanced HIV/HBV co-infected Thais is likely to be important [50] and no sustained change in the HBV-specific CD8+T cells response following HBV-active cART was observed in this population [57]. HIV significantly depletes CD4+ T-cells in the GI tract leading to increased microbial translocation as measured by circulating LPS and increased total levels of 16S ribosomal bacterial DNA (16rDNA) [52, 147, 148]. Therefore, the roles of microbial translocation and immune activation will be an important area for future study.

The role of vitamin D in chronic hepatitis B needs to be further explored. Vitamin D insufficiency could have a negative impact on calcium homeostasis, bone health, the immune system, inflammatory response, and fibrogenesis [59]. The finding of a high prevalence of vitamin D insufficiency in our HIV/HBV co-infected patients with mild liver fibrosis is somewhat worrisome. Our HIV/HBV co-infected patients require long term HBV-active drugs that include TDF, which can cause proximal tubular dysfunction [149-151], resulting in prolong phosphate wasting and osteopenia/osteoporosis. Apart from vitamin D supplementation, bone mass density, bone markers, and tubular function in HIV/HBV co-infection and HBV mono-infection will be important areas for future research. A recent study has found that HIV/HBV coinfected patients were 2.26 times more likely to develop chronic kidney disease than HIV-infected patients without HBV[152]. Future studies of new anti-HIV and anti-HBV agents with less renal and bone toxicity, for instance tenofovir alafenamide fumarate (TAF), a TDF pro-drug, in individuals HIV/HBV co-infection are warranted.

A significant proportion of our Thai patients with HIV/HCV co-infection had advanced liver fibrosis. Fortunately, there was a high proportion with favorable HCV genotype (47% with hepatitis C genotype 3 and 90% with IL28B CC genotype), indicating that if our patients receive treatment for HCV as soon as possible, advanced liver fibrosis and cirrhosis can be averted. At the present time, the Thai government has included pegylated interferon and ribavirin in the universal health coverage program.

Finally, HIV associated TB remains an important disease in resource-limited settings. We have shown that the use of nevirapine [100] as an alternative treatment in Thai individuals with HIV/TB co-infection and efavirenz toxicity is safe and effective. Although we have recently shown the efficacy of adjusted doses of boosted IDV and rifampicin [153], there is a need for newer drugs that have less drug interactions with rifampicin, especially in the setting of NNRTI treatment failure and unavailability of rifabutin. Lastly, we have proven the feasibility and efficacy of TST and isoniazid prophylaxis in our HIV-infected patients. Other studies have also confirmed the efficacy of IPT during the first 6 months of cART [140]. IPT should be implemented in HIV-infected patients living in high endemic areas of TB who have positive TST without any clinical symptoms and signs of active TB, particularly those with low CD4 cell counts[141].

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References


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