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Outcome of Isoniazid Preventive Therapy in Adults Living with HIV in Penang, Malaysia

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Abstract

Isoniazid preventive therapy (IPT) is a recommended strategy by World Health Organization (WHO) for prevention of active TB infection in people living with HIV. However, data on feasibility and outcome of IPT in Asia are limited. We conducted a retrospective study of 242 HIV patients in Penang who were commenced on IPT between 2011 and 2014, at two HIV specialist clinics in Penang General Hospital and Seberang Jaya Hospital. We evaluated the outcome of IPT in terms of completion rate, adverse events and incidence of active TB. A total of 193 (81.1%) patients completed 6 months of IPT. Patients receiving concurrent highly active antiretroviral therapy (HAART) had significantly higher IPT completion rate (86.1%) compared to those who were not on HAART (67.7%). Major reasons for non-completion were adverse events (21/45) and defaulting from follow-up (17/45). Forty patients (18%) developed adverse events, including hepatotoxicity (8.56%) and rash (5.41%). The risk factors for hepatotoxicity were Hepatitis B/C co-infection and alanine transaminase above the upper limit of normal at baseline. None of our patients who received IPT developed active TB up to 1 year of follow-up. IPT is feasible and relatively safe. Co-administration of IPT with HAART does not compromise safety or compliance.

Keywords: HIV; IPT; Isoniazid; Tuberculosis; Hepatitis

Introduction

HIV is the strongest risk factor for developing tuberculosis (TB) disease in those with latent or new mycobacterium tuberculosis infection. The risk of developing TB is between 20 to 37 times greater in people living with HIV (PLHIV) than among those who do not have HIV infection [1]. Morbidity and mortality from drug-sensitive and drug-resistant TB among PLHIV are unacceptably high [2,3].

Highly active antiretroviral treatment (HAART) significantly but not entirely reduces the risk of TB disease [4]. In HIV infected patients, isoniazid preventive therapy (IPT) reduces reactivation of latent TB infection, both in industrialized countries [5–7] as well as in developing countries [8-10]. In 1993, the World Health Organization (WHO) first issued a policy statement that recognized the efficacy of TB preventive therapy and recommended IPT for PLHIV [11-13]. The WHO recommended regimen for TB preventive therapy in PLHIV is isoniazid for at least 6 months [14].

The IPT program has since been implemented worldwide. The outcome of IPT has been predominantly determined in clinical trials and observational studies in African countries. Data on feasibility, efficacy, safety and completion rates of IPT among PLHIV in Asia are limited. There are specific concerns about adverse events of isoniazid in those with concurrent HAART.

Objectives

In this study we assessed the demographics and compliance of PLHIV taking IPT in two hospital-based HIV clinics in Penang, Malaysia. We also aimed to determine the rates and contributory factors of adverse events, as well as the incidence of active TB within 1 year after initiation of IPT.

Methodology

Study design and population

This retrospective cohort study was conducted at two HIV specialist clinics in Penang General Hospital and Seberang Jaya Hospital respectively, where IPT has been implemented since 2011. Subjects included HIV patients who were commenced on IPT between 2011 and 2014, with or without concurrent HAART.

Interventions

All subjects underwent TB symptom screening (fever, cough, weight loss and night sweats for the past 4 weeks) and further investigations (including chest X-ray) if indicated. Chest X-ray was not a mandatory screening before initiating IPT. Tuberculin skin test (Mantoux) was not required for IPT eligibility. After ruling out active TB, IPT consisting of isoniazid 300 mg and pyridoxine 20 mg daily was started for 6 month duration in accordance with WHO recommendations. HAART was initiated before, during or after IPT based on indication and clinical appropriateness. Follow-up visits during IPT were monthly to three monthly. Patients were monitored for TB symptoms, compliance and adverse events including elevated alanine transaminase (ALT). Upon completion of IPT, patients would resume routine HIV follow-up visits with regular screening of TB symptoms.

Outcome

The outcome of interest in this study was the IPT completion rate, incidence of adverse events and occurrence of active TB infection at 1 year follow-up. Patients who were lost to follow-up or expired (due to causes not related to IPT) were excluded from the adverse events and TB occurrence analysis. Patients who were transferred to other hospitals were excluded from all outcome analysis.

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Hepatotoxicity was defined as ALT level of at least 2 times the upper limit of normal (ULN) [15]. The severity of hepatotoxicity was graded based on a system defined by AIDS Clinical Trials Group (ACTG) (Table 1).

Data collection and analysis

Information on patient demographics, baseline characteristics (CD4 count, HAART regimen, ALT level, viral hepatitis co-infection etc.) and outcome was retrieved from patients' clinic records and data sheets. Data integrity was assessed and descriptive statistics were generated. Relative risks (RR) were determined for the cohort analysis of IPT non-completion and adverse events.

Results

We started IPT for 242 patients, of whom 204 (84.3%) were males and their mean age was 37.4 ± 10.9 years. Their median baseline CD4 count was 315.5 cells/uL (IQR, 327); 31.4% had a CD4 count less than 200 cells/uL and 72.7% were receiving HAART during IPT. Baseline chest X-rays were done for 85 (35.1%) patients. Majority of patients (229/242, 94.6%) had normal baseline ALT level (<ULN), while 12 (5%) patients had slightly higher ALT level (1-1.9 x ULN) at the start of IPT. Only 1 patient had baseline ALT more than 2 times the ULN. Twenty nine (12%) patients were co-infected with viral hepatitis (10 had Hepatitis B, 18 had Hepatitis C, and 1 had both Hepatitis B and C) (Table 2).

HAART regimens that patients received consisted of Tenofovir-Emtricitabine, Efavirenz (67.1%), Zidovudine- Lamivudine, Efavirenz (14.2%), Zidovudine-Lamivudine, Nevirapine (7.4%), Tenofovir-Emtricitabine, Raltegravir (4.6%) and others (Table 3).

Completion Rate

Excluding patients who were transferred to other hospitals, 193 (81.1%) patients completed IPT (Table 4). Major reasons for non-completion of IPT were adverse events (46.7%), defaulting from follow-up (37.8%) and poor compliance (6.7%). One patient passed away during 2nd month of IPT due to septic shock, which was not related to TB or IPT. Another patient had interruption of IPT medications due to prescription error. One patient stopped IPT due to pill burden (he was receiving concomitant HAART) and another was worried about side effects (Figure 1).

Completion rate was higher among patients with concurrent HAART (149/173, 86.1%) compared to HAART naïve patients (44/65,67.7%) (P=0.001). Co-administration of HAART significantly reduced the incidence of non- completion of IPT (RR, 0.43; 95% confidence interval [CI], 0.3-0.7; P<0.005). Age greater than 35 years, male gender and CD4 count less than 200 cells/uL were not associated with non-completion of IPT (Table 5).

Adverse Events

Forty patients (18%) developed adverse events during IPT (Table 4). There were 19 incidences of hepatotoxicity, 12 rashes, 6 gastrointestinal (GI) symptoms (diarrhea, nausea), 5 peripheral neuropathy and 2 central nervous system (CNS) symptoms (sleepiness, lightheadedness) (Figure 2).

The incidence rate of hepatotoxicity was 8.56%. Significant risk factors for hepatotoxicity during IPT were Hepatitis B and/or C co-infection (RR, 3.99; 95% CI, 1.7-9.4; P<0.01) and baseline ALT level ≥ ULN (RR, 8.85; 95% CI, 4.1-19.0; P<0.001). Concurrent HAART, age greater than 35 years, male gender and CD4 count less than 200 cells/uL were not associated with the occurrence of hepatotoxicity (Table 6).

Feature	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT (ULN)	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
AST (ULN)	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
Alkaline Phosphatase (ULN)	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
GGT (ULN)	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
Bilirubin (ULN)	Normal	>1.0-1.5	>1.5-2.5	>2.5-5	>5

Table 1: AIDS Clinical Trials Group (ACTG) Severity Grading of Drug Induced Liver Injury.

Baseline Covariates	N=242; No. (%)
Number of patients	
Penang General Hospital	210 (86.8%)
Seberang Jaya Hospital	32 (13.2%)
Age (years) [Mean=37.4 ± 10.9]	
≤ 35	109 (45.0%)
>35	133 (55.0%)
Gender	
Male	204 (84.3%)
Female	38 (15.7%)
Race	
Chinese	129 (53.3%)
Malay	63 (26.0%)
Indian	38 (15.7%)
Other	12 (5.0%)
CD4 Count (cells/uL) [Median=315.5, IQR, 327]	
<200	76 (31.4%)
200-349	59 (24.4%)
350-499	52 (21.5%)
500 & above	55 (22.7%)
Concurrent HAART	
Yes	176 (72.7%)
No	66 (27.3%)
Baseline Chest X-Ray	
Done	85 (35.1%)
Not done*	157 (64.9%)
Baseline ALT	
<ULN	229 (94.6%)
1 – 1.9 x ULN	12 (5.0%)
2 – 2.9 x ULN	1 (0.4%)
Viral Hepatitis co-infection	
No	213 (88.0%)
Hepatitis B	10 (4.2%)
Hepatitis C	18 (7.4%)
Hepatitis B and C	1 (0.4%)
HAART: Highly Active Antiretroviral Therapy; ULN: Upper limit of Normal; *Chest X-ray was not a mandatory screening before initiating IPT	

Table 2: The socio-demographic and baseline characteristics of study cohort.

The severity of liver injury sustained was either Grade 1 (6 patients) or Grade 2 (13 patients), all of which were asymptomatic and reversible. Ten patients (52.6%) out of those who developed hepatotoxicity managed to complete IPT without complication despite significant elevation of ALT level (Table 7).

Skin rash occurred at a rate of 5.41%. There was no significant predisposing factor for the development of rashes (Table 8). No correlation analysis was done for other adverse events as the incidence was low.

N = 176; No. (%)		
Timing of HAART commencement	Before IPT	158 (89.8%)
	During IPT	18 (10.2%)
	Tenofovir-Emtricitabine (FDC), Efavirenz	118 (67.1%)
	Zidovudine-Lamivudine (FDC), Efavirenz	25 (14.2%)
	Zidovudine-Lamivudine (FDC), Nevirapine	13 (7.4%)
	Tenofovir-Emtricitabine (FDC), Raltegravir	8 (4.6%)
	Tenofovir-Emtricitabine (FDC), Lopinavir-Ritonavir (FDC)	3 (1.7%)
HAART Regime	Tenofovir-Emtricitabine (FDC), Nevirapine	2 (1.1%)
	Stavudine-Lamivudine-Nevirapine (FDC)	3 (1.7%)
	Tenofovir-Emtricitabine (FDC), Rilpivirine	2 (1.1%)
	Others	2 (1.1%)
FDC: Fixed Dose Combination		

Table 3: Concurrent HAART during IPT.

Outcomes		**No. (%)**
N=242		
Defaulted IPT and lost to follow-up		15 (6.2%)
Expired during IPT		1 (0.4%)
Transferred to other hospitals during IPT		4 (1.7%)
N=238		
Completed IPT*	Yes	193 (81.1%)
	No	45 (18.9%)
N=222		
Adverse events during IPT**	Yes	40 (18%)
	No	182 (82%)
N=222		
Occurrence of active TB infection at 1 year follow-up**	Yes	0 (0%)
	No	222 (100%)
*Excluding patients who were transferred to other hospitals during IPT; **Excluding patients who were lost to follow-up, expired and transferred to other hospitals during IPT		

Table 4: Summary of study outcomes.

TB Occurrence

None of the patients who were exposed to IPT (including those who stopped IPT prematurely) developed active TB infection at 1 year follow-up (Table 4).

Sub-analysis on cohort who were lost to follow-up

There were 15 (6.2%) patients who lost to follow-up during IPT. This was significantly associated with patients co-infected with Hepatitis C (RR, 3.73; 95% CI, 1.4-9.8; P<0.05). Patients with concurrent HAART were less likely to be lost to follow-up (RR, 0.25; 95% CI, 0.1-0.6; P<0.01). There was no clear association with age, gender or baseline ALT (Table 9).

Discussion

Studies have consistently shown early initiation of HAART and immune reconstitution prolongs life expectancy of HIV patients, to the extent of approaching that of general population [16]. The START (Strategic Timing of Anti- Retroviral Treatment) study, a large-scale randomized clinical trial has established that early antiretroviral treatment at CD4 count above 500 cells/uL significantly reduces the rates of serious AIDS and non-AIDS events [17]. Many HIV guidelines including the WHO have been revised to recommend early initiation of HAART regardless of presenting CD4 cell count or clinical stage [18].

In our study, 72.7% of our patients were started on HAART before or during IPT. As majority of HIV patients are receiving HAART, it is important to study the outcome of co-administration of IPT with HAART in terms of compliance and adverse events.

The overall completion rate of IPT in our study was acceptable and comparable to previous studies. Despite the increase in pill burden, IPT was well tolerated with concurrent HAART. In fact, there was a significantly higher completion rate in patients with concurrent HAART. We attributed this observation to the pre-HAART counseling

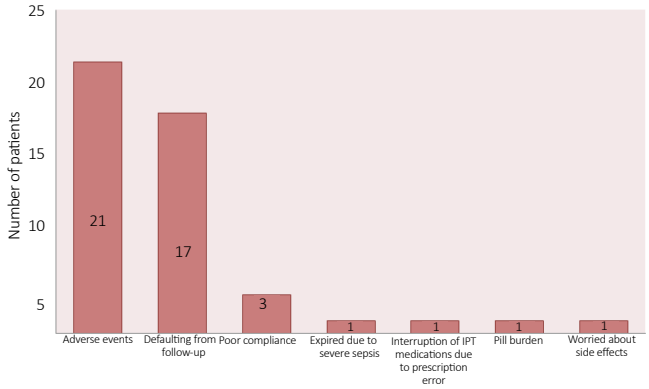

Figure 1: Reasons for non-completion of PTI.

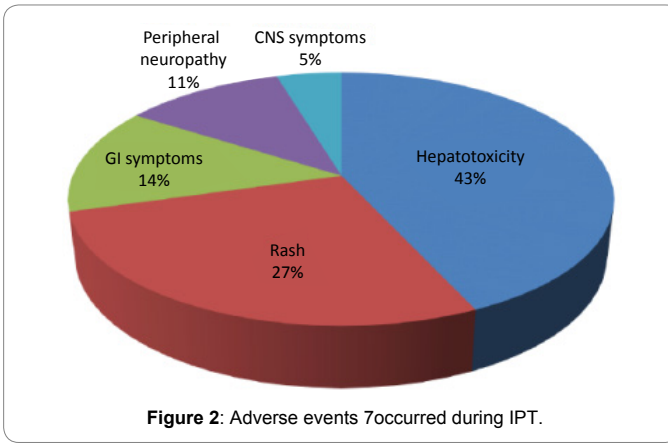

Figure 2: Adverse events 7occurred during IPT.

	Fraction of patients with non-completion of IPT	**RR (95% CI)**	**P value**
Age			
>35	24/130	0.95 (0.6-1.6)	0.979
≤ 35	21/108	1	
Gender			
Male	39/201	1.20 (0.6 - 2.6)	0.821
Female	6/37	1	
CD4 count			
< 200	15/75	1.09 (0.6 - 1.9)	0.909
≥ 200	30/163	1	
Concurrent HAART			
Yes	24/173	0.43 (0.3 - 0.7)	<0.005
No	21/65	1	
HAART: Highly Active Antiretroviral Therapy			

Table 5: Risk factors associated with non-completion of IPT.

Fraction of patients with hepatotoxicity*		RR (95% CI)	P value
Age			
>35	10/120	0.94 (0.4 -2.2)	0.912
≤ 35	9/102	1.0	
Gender			
Male	17/189	1.48 (0.4 -6.0)	0.827
Female	2/33	1.0	
CD4			
CD4 <200	7/68	1.32 (0.5 -3.2)	0.723
CD4 ≥ 200	12/154	1.0	
Baseline ALT			
≥ ULN**	6/11	8.85 (4.1 -19.0)	<0.001
<ULN	13/211	1.0	
Concurrent HAART			
Yes	13/166	0.73 (0.3 -1.8)	0.696
No	6/56	1.0	
Hep B/C co-infection			
Yes	6/23	3.99 (1.7-9.4)	<0.01
No	13/199	1.0	

ALT: Alanine Transaminase; ULN: Upper Limit of Normal; HAART: Highly Active Antiretroviral Therapy; *Elevated ALT level of at least 2x ULN; ** Patients with ALT level of 1-1.9x ULN; HAART=Highly Active Antiretroviral Therapy; *Elevated ALT level of at least 2x ULN; ** Patients with ALT level of 1-1.9 x ULN

Table 6: Risk factors associated with hepatotoxicity during IPT.

No	Age	Gender	Baseline CD4 count (cells/uL)	Concurrent HAART	Exposure to NNRTIs	Viral Hepatitis Co-infection	Baseline ALT (Relative to ULN)	Highest elevated level of ALT (Relative to ULN)*	Grade of Severity**	Completed IPT
1	40	M	101	Yes	NVP	No	<ULN	2.9 x	2	No
2	38	M	84	Yes	EFV	Hep C	<ULN	4 x	2	No
3	37	M	18	Yes	EFV	No	<ULN	2 x	1	Yes
4	32	M	534	No	No	No	<ULN	3.5 x	2	Yes
5	38	M	36	Yes	EFV	No	<ULN	2.2 x	1	Yes
6	33	M	449	No	No	No	<ULN	4.6 x	2	No
7	37	M	147	Yes	EFV	Hep B	<ULN	2.6 x	2	Yes
8	28	M	414	Yes	EFV	No	<ULN	2.6 x	2	No
9	34	M	419	No	No	Hep C	<ULN	2.2 x	1	Yes
10	34	M	550	Yes	EFV	Hep B & C	<ULN	2.9 x	2	Yes
11	42	M	12	Yes	EFV	No	1 x	2.6 x	2	Yes
12	25	M	274	Yes	EFV	No	<ULN	4 x	2	No
13	30	M	345	Yes	EFV	No	<ULN	3.8 x	2	No
14	27	M	627	No	No	No	1.4 x	3.1 x	2	No
15	61	F	437	No	No	No	<ULN	3.8 x	2	Yes
16	45	M	141	Yes	EFV	Hep C	1 x	2 x	1	Yes
17	33	M	300	Yes	EFV	No	1.4 x	2.1 x	1	Yes
18	37	F	300	Yes	No	No	1.9 x	2.5 x	1	No
19	48	M	636	No	No	Hep C	1 x	2.7 x	2	No

M: Male; F: Female; HAART: Highly Active Antiretroviral Therapy; NNRTIs: Non-nucleoside Reverse Transcriptase Inhibitors; EFV: Efavirenz; NVP: Nevirapine; ALT: Alanine Transaminase; ULN: Upper Limit of Normal; *Hepatotoxicity was defined as elevation of ALT level ≥ 2 x ULN; **Based on Severity Grading of Drug Induced Liver Injury by AIDS Clinical Trials Group (ACTG) All hepatotoxicity were asymptomatic and reversible after stopping or completing IPT.

Table 7: Characteristics of study cohort who developed hepatotoxicity during IPT (N=19).

which emphasized on strict drug adherence. Most of these patients were mentally prepared and committed to be on long term medications.

Although the benefit of IPT among PLHIV is well established, there were concerns about adverse events of isoniazid, particularly when co-administered with HAART. Isoniazid and NNRTI (non-nucleoside reverse transcriptase inhibitor), a commonly used class of antiretroviral drug, shared similar side effect profiles. They are known to cause hepatotoxicity and rash. A prospective study in Botswana of 1,995 PLHIV on IPT observed 1.1% rate of severe isoniazid-associated hepatitis, which was similar to rates in HIV-uninfected populations. HAART was received by 480 participants but was not statistically associated with isoniazid induced hepatitis (RR, 1.56; 95% CI, 0.62-3.9) [19]. A South African study of 818 men and 50 women reported no statistically significant association between Grade 3 or 4 hepatitis in PLWH receiving IPT and efavirenz based anti-retroviral therapy

Fraction of patients with skin rash		RR (95% CI)	P value
Age			
>35	4/120	0.42 (0.1 - 1.3)	0.237
≤ 35	8/102	1.0	
Gender			
Male	12/189	- (∞ - 0.0)	0.284
Female	0/33	1.0	
CD4			
CD4 <200	5/68	1.62 (0.5 - 4.9)	0.596
CD4 ≥ 200	7/154	1.0	
Concurrent HAART			
Yes	8/166	0.67 (0.2 - 2.2)	0.747
No	4/56	1.0	
HAART: Highly Active Antiretroviral Therapy			

Table 8: Risk factors associated with skin rash during IPT.

Fraction of patients who lost to follow- up		RR (95% CI)	P value
Age			
>35	8/128	0.97 (0.4 - 2.6)	0.831
≤35	7/109	1.0	
Gender			
Male	12/201	0.72 (0.2 - 2.4)	0.868
Female	3/36	1.0	
CD4			
CD4 < 200	6/74	1.47 (0.5 - 4.0)	0.638
CD4 ≥ 200	9/163	1.0	
Concurrent HAART			
Yes	6/172	0.25 (0.1 - 0.6)	<0.01
No	9/65	1.0	
Baseline ALT			
≥ ULN	2/12	2.88 (0.7 - 11.4)	0.368
< ULN	13/225	1.0	
Hep C co-infection*			
Yes	5/28	3.73 (1.4 - 9.8)	<0.05
No	10/209	1.0	

Table 9: Risk factors associated with patients lost to follow-up during IPT.

(hazard ratio,0.83, 95% CI, 0.20–3.4) [20]. These observations were consistent with our study finding that patients concomitantly taking HAART and IPT had no significantly increased risk of hepatotoxicity (RR, 0.73; 95% CI, 1.8-0.3), despite majority of them were on NNRTI (efavirenz or nevirapine) based HAART. In addition, all our reported hepatotoxicity was either mild or moderate (severity Grade 1 to 2) and reversible. More than half of our patients with elevated ALT managed to complete IPT without any complications. The incidence of skin rash was low and not associated with co-administration of HAART.

Patients with Hepatitis B/C co-infection or baseline ALT more than ULN had to be closely monitored for risk of hepatotoxicity as shown in our study. However, these patients should not be denied IPT as the benefit still outweighed the risk.

Majority of our cohort had baseline CD4 count less than 350 cells/uL and HAART was strongly indicated. Thirty- one point four percent (31.4%) of them had CD4 count less than 200 cells/uL, which rendered them very susceptible to TB reactivation. A meta-analysis of randomized clinical trials that assigned 7619 HIV patients to IPT or placebo found an overall 35% of TB risk reduction (RR,0.65, 95% CI, 0.51-0.84) in all participants [21]. Our cohort who received IPT did not develop active TB infection up to 1 year of follow-up. However, we could not attribute this finding solely to IPT as this was not a comparative study against IPT naïve patients and most of our patients were co-administered with HAART. It is well accepted that immune reconstitution after HAART reduced the risk of reactivation of TB. In a cohort study in South Africa, the number of TB cases averted by HAART was greatest in patients with WHO stage 3 or 4 (18.8 averted cases per 100 patient-years, adjusted rate ratio 0.22 [0.09–0.41]; p=0.03) and in those with CD4 count of less than 200 cells/μL (14.2 averted cases per 100 patient-years, adjusted rate ratio 0.18 [0.07–0.47]; p<0.0001) [4]. In addition, evidence from two retrospective studies that examined the benefit of TB prevention in PLHIV receiving HAART and IPT indicated that the protection conferred by the combination was additive [22,23].

Six point two percent (6.2%) of patients were lost to follow-up during IPT. A significant proportion of these patients were co-infected with Hepatitis C. They comprised of ex-intravenous drug users with poor social- economic background and in general have a tendency to default treatment. We also suspect a few of them may have developed adverse events, which led to self-discontinuation of IPT and subsequent were lost to follow-up. The phenomenon of patients with concurrent HAART having significant lower risk of defaulting follow-

up likely reflects the effectiveness and importance of our pre-HAART counseling.

Although international guidelines on the timing of initiation of IPT and HAART are unsettled, we suggest that IPT can precede HAART initiation if a patient's CD4 count is still high (more than 350 cells/uL). Commencing IPT first would allow HAART naïve patients to undergo pill training prior to initiation of HAART, which requires life-long drug adherence and compliance. Conversely, in patients with low CD4 count (less than 350 cells/uL) or have previous opportunistic infections, immune reconstitution should be the priority. Hence IPT should be deferred until stabilization on HAART.

Conclusion

IPT is feasible and relatively safe among our local PLHIV. IPT and HAART can be co-administered to give additive prophylaxis against reactivation of TB and has not been shown to compromise safety or compliance in our study. Larger and longer comparative studies are needed to determine the outcome of IPT in our local HIV population. Other potential risk factors of isoniazid-hepatotoxicity such as alcohol and bactrim usage should be evaluated. Future studies also need to address the risk of developing drug-resistant TB after exposure to IPT.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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