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Isoniazid Preventive Therapy Completion in the Era of Differentiated HIV Care

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INTRODUCTION

Isoniazid preventive therapy (IPT) reduces incidence of TB by up to 60% and reduces mortality among people living with HIV (PLWH),[1–4] but implementation of IPT remains poor. In East Africa, use of IPT by patients in HIV care ranges from 0.5% in Uganda to 19% in Kenya.[5] Even where IPT programs are implemented, completion rates in East Africa range between 36–98%.[6–11] Countries in sub-Saharan Africa are scaling up both IPT and differentiated HIV care, but there is little data to guide optimal integration of IPT into differentiated HIV care models.

In differentiated HIV care stable patients typically receive quarterly ART refills either in a clinic or via community adherence groups to enhance retention in care and to decongest clinics.[12,13] This less frequent scheduling is at odds with guideline recommended monthly IPT visit frequencies and could challenge successful IPT completion. To our knowledge, there are no studies assessing IPT treatment completion in the setting of well-engaged patients receiving differentiated HIV care. As such, we sought to characterize (1) baseline IPT completion rates and (2) predictors of IPT completion among HIV-infected adults, with a high rate of virologic suppression, who were receiving differentiated HIV care in 5 rural

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clinics in Uganda. These patients were accustomed to quarterly visits for ART refills, but to receive IPT, had to increase their visit frequency to monthly.

METHODS

From January through April 2016, we screened a convenience sample of 137 HIV-infected adults from 5 communities participating in the SEARCH HIV test and treat trial (NCT01864603) for IPT eligibility. All participants were receiving differentiated HIV care consisting of nurse triage, quarterly ART visits, and patient-centered care at five government-sponsored clinics in rural Uganda.[15] Screening and frequency of clinic visits for IPT were conducted per Uganda Ministry of Health (MOH) guidelines.[14] Patients started on IPT (INH with B6) returned to clinic for a 2-week assessment for possible side effects and then monthly thereafter for 5 months. At the monthly visit clinicians provided IPT refills and assessed patient adherence and side effects. Patients who received IPT could choose to continue to receive ART and cotrimoxazole refills quarterly or monthly.

Our primary outcome was completion of IPT, defined as a patient picking up their 5th IPT refill. Exposures of interest were obtained during the SEARCH trial and included socioeconomic variables (gender, age, education, and wealth); IPT-specific barriers (reported side-effects within 2 weeks of IPT initiation); and HIV clinical variables (viral suppression). Wealth tertiles were generated from a principal component analysis derived from a household asset questionnaire. Pre and post IPT viral loads were obtained during the SEARCH trial's community-wide health campaigns (CHC).[16,17] Pre-IPT viral load was defined as the most recent measurement within a year prior to IPT initiation. Post-IPT initiation viral load was defined as a viral load measured within 6 months after IPT initiation and was available for the subset of patients with a viral load measured at a CHC by database closure on March 10, 2017. Viral suppression was defined as a viral load <500 copies/ml. CD4 cell count was collected from community-wide SEARCH health campaigns from 2015–2016.

Logistic regression was used to calculate unadjusted and adjusted odds ratios (aOR) for IPT completion. Predictors with a bivariate p-value ≤ 0.1 were included in the multivariate model. Wealth was included in the multivariate model *a priori* given associations between IPT adherence and cost of health care access.[18,19]

The SEARCH study was approved by the ethical review boards of Makerere University, the Uganda National Council of Science and Technology (Kampala, Uganda), the Kenya Medical Research Institute (Nairobi, Kenya), and the University of California, San Francisco (San Francisco, CA, USA).

RESULTS

Of the 137 HIV-infected adults screened for IPT, 134 (98%) were eligible and 133 (97%) initiated treatment. Pre- and post- IPT initiation viral loads were measured on 86% (114/133) and 77% (102/133) of IPT initiators, respectively. CD4 count was available for 93% (124/134) of patients. Among patients who initiated IPT, the median age was 41 years (IQR:33–46). 76% of participants were female. The median CD4 count was 520 cells/μL

(IQR: 404–678). Median time since ART initiation was 2.3 years (IQR1.7–3.7). 15% (20/133) of patients reported a side effect at the 2-week clinic assessment. The most common side effect experienced by patients starting IPT was dizziness (13, patients, 10%). Five patients (4%) reported numbness, 3 (2%) reported nausea, 3 (2%) reported diarrhea, 2 (1.5%) reported abdominal pain, 1 reported itching, 1 reported generalized weakness, 1 reported headache, and 1 reported face swelling. There were no reports of jaundice, dark urine, or pale stools.

Overall, 98 (73%) of the 133 participants who initiated IPT completed treatment. Of the 133 patients who started IPT, 132 (99%) attended their 2-week visit. Of the 35 patients who did not complete IPT, 6 (17%) stopped during the first two weeks, 20 (60%) stopped between two weeks and three months of treatment, and (26%) stopped after 3 months of treatment. Half of the patients who reported side effects at 2 weeks completed IPT. The adjusted odds of IPT completion was higher among older patients (compared to younger patients) and patients who did not report side effects (compared to those who reported effects) (Table 1). The odds of IPT completion was higher among patients from the highest wealth tertile compared to those from the lowest wealth tertile, though this trend was only significant in the unadjusted model.

Among the 89 patients with both a viral load pre- and post-IPT initiation, viral suppression was 94% pre- and 97% post-IPT initiation (p=0.41). Among the 102 patients with a post-IPT viral load available, 73 (72%) achieved both IPT completion and viral suppression.

DISCUSSION

In summary, we found that 73% of patients completed IPT and that viral suppression remained high after initiating IPT. Though the majority of patients in our study completed IPT, there remains room for improvement especially among younger patients and those reporting side effects. Although prior research has shown that patients on ART are more likely to adhere to IPT,[8,9] our findings suggest that in a sample of highly ART adherent patients in differentiated care, barriers to IPT completion persist.

The proportion of patients completing IPT in our study is lower than in studies of patients on ART who are receiving non-differentiated HIV care in East Africa. In the Democratic Republic of Congo and Ethiopia IPT completion among patients on ART was 89%[8] and 86%,[9]respectively. One possible explanation for this difference is that some patients in differentiated care may perceive the costs associated with increased visit frequency for IPT to outweigh the benefits of IPT, and they in turn may prioritize collecting ART over IPT refills. The cost of accessing health care is a barrier to both IPT and ART adherence,[18,19] and further study is warranted to assess whether harmonizing IPT refills with quarterly ART refills will further improve IPT adherence among patients receiving differentiated HIV care.

At the same time, early visits within 2–4 weeks of IPT initiation are important to assess tolerance to isoniazid. In our study, 15% of patients reported some side effects at the 2-week assessment, and half of those patients did not complete treatment. IPT delivery may require “differentiated” care strategies for patients with early side effects and possible safety

concerns, which may include follow up phone calls or changes in visit frequency. Additional counseling and support by healthcare providers may be enough to encourage patients with mild or moderate side effects to continue with their IPT treatment when they may have otherwise been inclined to stop. Additionally, providers may benefit from additional training on how to assess which side-effects are severe enough to warrant treatment discontinuation. Implementation of IPT on a broader scale should include programmatic interventions that specifically address and mitigate side effects so that patients can complete their treatment.

Our study has some limitations. Convenience sampling may have resulted in a sample of patients more likely to adhere to IPT than the broader population, and the low proportion of men and younger patients may limit generalizability. Viral load testing coverage was not complete, so our estimate may overestimate viral suppression. However, if we assume all missing pre-IPT viral loads were detectable, then viral suppression is still high at 80% (106/133). The relatively small sample size may limit our precision and ability to detect predictors of IPT completion. However, despite the small sample size, to our knowledge this study is the first of its kind to report findings on IPT completion in differentiated care and these findings may inform larger studies and ongoing scale-up of IPT in differentiated care settings.

Differentiated care calls for a client-centered approach that responds and adapts to the patient's specific needs. Whether aligning the frequency of clinic visits or finding new modes of delivery, IPT must be implemented in such a manner that maintains safety while maximizing treatment completion. As countries begin to implement IPT more broadly, it is critical to further explore ways to optimize integration of TB prevention and differentiated HIV care for our patients.

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TABLE 1

Bivariate and multivariate predictors of completing 6 months of isoniazid preventive therapy (IPT) among 133 patients receiving differentiated HIV care in 5 rural clinics in Eastern Uganda. The multivariate model is restricted to the 119 patients with complete data for age, wealth index, and side effects.

	IPT Completion	IPT Completion
	Unadjusted OR (95% CI) p-value	**Adjusted OR (95% CI) p-value**
Female	0.6 (0.3–1.2) p = 0.133	–
Married	1.0 (0.8–1.1) p = 0.625	
Age		
15–38 years (ref)		
39–46 years	**3.5 (2.8–4.3) p = 0.000**	**4.9 (3.8–6.2) p = 0.000**
47 years +	**3.4 (1.3–8.8) p = 0.013**	**4.2 (1.3–13.8) p = 0.019**
Any Education (primary education and above)	1.4 (0.7–3.1) p = 0.354	
Wealth Index		
Wealth tertile 1 (ref)	–	–
Wealth tertile 2	1.2 (0.7–2.1) p = 0.457	0.9 (0.3–2.2) p = 0.745
Wealth tertile 3	**2.0 (1.2–3.3) p = 0.010**	1.5 (0.7–3.6) p = 0.317
Side effects (in first 2 weeks)	**0.3 (0.1–0.6) p < 0.001**	**0.2 (0.1–0.4) p < 0.001**
Pre-IPT HIV viral suppression (HIV RNA<500 copies /ml)	1.1 (0.1–15.6) p = 0.922	

IPT= Isoniazid Preventive Therapy; OR= odds ratio; CI= confidence interval

* Confidence intervals accounted for clustering by clinics and robust standard errors