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Completion of isoniazid preventive therapy among human immunodeficiency virus positive adults in urban Malawi

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SUMMARY

SETTING: Despite worldwide scale-up of human immunodeficiency virus (HIV) care services, relatively few countries have implemented isoniazid preventive therapy (IPT). Among other programmatic concerns, IPT completion tends to be low, especially when not fully integrated into HIV care clinics.

OBJECTIVE: To estimate non-completion of 6-month IPT and its predictors among HIV-positive adults aged ≥16 years.

DESIGN: A prospective cohort study nested within a cluster-randomised trial of TB prevention was conducted between February 2012 and June 2014. IPT for 6 months was provided with pyridoxine at study clinics. Non-completion was defined as loss to follow-up (LTFU), death, active/presumptive TB or stopping IPT for any other reason. Random-effects logistic regression was used to determine predictors of non-completion.

RESULTS: Of 1284 HIV-positive adults initiated on IPT, 885/1280 (69.1%) were female; the median CD4 count was 337 cells/µl (IQR 199–511); 320 (24.9%) did not complete IPT. After controlling for antiretroviral treatment status, IPT initiation year, age and sex, non-completion of IPT was associated with World Health Organization stage 3/4 (aOR 1.76, 95%CI 1.22–2.55), CD4 count 100–349 cells/µl (aOR 1.93, 95%CI 1.10–3.38) and any reported side effects (aOR 22.00, 95%CI 9.45–46.71).

CONCLUSION: Completion of IPT was suboptimal. Interventions to further improve retention should target immunosuppressed HIV-positive adults and address side effects.

KEY WORDS: tuberculosis; loss to follow-up; risk factors; prospective; sub-Saharan Africa

TUBERCULOSIS (TB) IS A GLOBAL public health threat, with a quarter of the population estimated to be latently infected worldwide.1 In 2015, the World Health Organization (WHO) estimated that there were 10.4 million incident TB cases and 1.4 million TB deaths globally.2 Approximately 11–13% of incident TB cases are co-infected with the human immunodeficiency virus (HIV).2–4 HIV-associated TB is highest in the WHO African Region, with HIV prevalence in TB patients exceeding 50% in some parts of southern Africa.2,5,6

Isoniazid (INH) preventive therapy (IPT) reduces the overall risk of TB in HIV-infected individuals by 35%, with greater reduction among tuberculin skin test (TST) positive individuals (pooled relative risk of 52%).7 When IPT is combined with antiretroviral treatment (ART), there is a multiplicative protective effect.6,8,9 Since the late 1990s, at least 6 months of IPT has been recommended by the WHO for HIV-positive individuals. Guidelines from 2015 now recommend no less than 36 months for people without symptoms of active TB, irrespective of CD4 count, availability of TST, ART status or pregnancy.10–12 In high TB incidence, resource-constrained settings, absence of current cough, fever, night sweats and weight loss can be used as a screening tool for IPT eligibility.13–16 IPT provision should be supported by regular adherence support and monitoring, and ideally accompanied by pyridoxine to reduce the risk of symptomatic peripheral neuropathy.17

Barriers to the uptake and completion of IPT have been widely reported, and include longer regimens,18,19 lack of health worker training and patient education on treatment guidelines,18,20 distance from the clinic and incompletely integrated HIV-TB care.20,21 In Malawi, the first wide-scale use of IPT

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by the national HIV programme was not implement-
ed until 2015. Lack of nationwide implementation
was initially driven by concerns from the
National TB Programme around the theoretical risk
of inducing INH resistance, given the difficulties of
excluding active TB disease, and historically low
completion rates under stand-alone IPT services.21,23
Experience, however, suggests little impact on drug
resistance patterns in practice.15 From the perspective
of HIV programmes, ongoing concerns have included
the cost and logistics of adding one (INH) or two
.plus pyridoxine) drugs to already overstretched HIV
care programmes, with the increasing pill burden and
side-effect profile potentially having a deleterious
impact on ART adherence, and the limited evidence
of broader health benefits beyond TB prevention.
Understanding the factors associated with non-
completion of IPT could therefore help accelerate
wider implementation, and inform strategies to
improve both the uptake and completion of IPT at
the programme level.

The main aims of the present study were to
estimate non-completion of IPT and determine its
predictors among HIV-positive adults initiating a 6-
month course of IPT delivered in urban Blantyre by a
research project before national roll-out.

MATERIALS AND METHODS
Study design and participants
This was a prospective cohort study nested within the
intervention arm of a community cluster randomised
trial of TB prevention (HiTB: ISRCTN20040005)
conducted between February 2012 and June 2014. In
the parent trial, community-based HIV testing and
TB active case finding were offered in the 14 urban
intervention communities comprising 16,660 adult
residents, while 14 control communities received TB
active case finding only. The trial profile and HIV
care clinic for confirmatory HIV testing and coun-
elling (HTC), WHO clinical staging assessment,
CD4 count measurement, and linkage to HIV and TB
care and prevention services, including IPT, all of
which were completed by study nurses. Eligible
participants for this cohort study were HIV-positive adults aged
≥16 years who were resident within intervention neighbourhood clusters in urban Blantyre, Malawi, and who initiated IPT as part of trial interventions. During clinic assessment, participants were assessed for IPT eligibility using a symptom screening tool, with the presence of any of cough,
fever, weight loss or night sweats prompting clinical
assessment and investigation for active TB. Participants without TB symptoms and weighing ≥35 kg
were offered 300 mg INH and 25 mg pyridoxine once
a day for 6 months to minimise the risk of INH
peripheral neuropathy. IPT was, however, stopped in
patients who developed neuropathy without attempt-
ing to distinguish the causative agent.

Follow-up and outcome measurement
IPT was dispensed separately from ART, such that
patients also receiving ART had to visit a second
clinic room within the same facility for their repeat
IPT prescriptions and final follow-up on months 1, 2,
3, 4, 5 and 6. IPT follow-up visits were harmonised as
far as possible with other HIV care clinic appoint-
ments, but in some instances a special IPT visit was
required. Adherence to IPT was monitored through
monthly prescription refill records. During IPT clinic
visits, participants were screened for TB symptoms
(and investigated if required), and assessed for
adverse events. The main emphasis was on early
detection of clinical hepatitis and peripheral neurop-
athy through systematic enquiry for jaundice, nausea
or vomiting, or any symptoms of peripheral neurop-
athy. All toxicities that led to IPT being temporarily
or permanently discontinued, and all grade 3 or 4
toxicity effects,26 were recorded in participant-held
treatment cards as well as in clinic registers.

Participants with serious adverse events (SAEs)
were referred to Queen Elizabeth Central Hospital,
Blantyre, for clinical management. SAEs and other
adverse events were documented and reported to the
Malawi College of Medicine Research Ethics Com-
mittee (COMREC), Blantyre, by the principal inves-
tigator (PI). Participants who died were followed up
by verbal autopsy through a community liaison
system of the parent trial, to ascertain the cause of
death. IPT was given on a monthly basis, and
participants who did not make all six clinic visits to
refill INH due to loss to follow-up (LTFU), death,
active/presumptive TB or having stopped treatment
for any other reason, were classified as not having
completed IPT. Home tracing for participants lost to
follow-up was not conducted.

Data collection and analysis
Study participant IPT registers were used to record
baseline demographics, clinical characteristics and
monthly outcomes. Data from the IPT registers were
extracted using an optical character-recognition
system, and imported into the study database.
Descriptive statistics were used to characterise study
participants, and to estimate the proportion of
participants lost from IPT, stratified by clinical and
socio-demographic characteristics. Age, sex, baseline
WHO stage, CD4 count, ART status, provider of
HTC service, reported past anti-tuberculosis treat-
ment, year of IPT initiation and side effects were
considered to be potential predictors of non-comple-
tion of IPT. All potential predictors were evaluated
for inclusion in a multivariate model, with age and sex included a priori. The final multilevel logistic regression model adjusted for patient characteristics, and a random-effect term to account for clustering by participant neighbourhood of residence. Analysis was carried out using Stata v14.0 (StataCorp, College Station, TX, USA) and R v3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics consideration
The parent study protocol was approved by the COMREC, Blantyre, and the London School of Hygiene & Tropical Medicine, London, UK. Participants provided written (or witnessed thumbprint) informed consent for HIV testing interventions, and verbal consent to initiate IPT as part of routine clinical care.

RESULTS
Characteristics of study participants
Of the 16,660 adult residents of the 14 intervention clusters, 14,004 (84.1%) underwent study HIV testing and 1725 (12.3%) were confirmed to be HIV-positive. Of the 1557/1725 (90.3%) HIV-positive participants screened for IPT eligibility, 1301 (83.6%) met the IPT eligibility criteria. Non-screening of 168 individuals was due to unavailability. Non-eligibility of those screened was due to presumptive TB (212/256, 82.8%), active TB (14/256, 5.5%), epilepsy (11/256, 4.3%), high alcohol intake (10/256, 3.9%), previous reaction to IPT (6/256, 2.3%) and known liver disease (3/256, 1.2%). A further 17 participants declined IPT, resulting in an IPT initiation rate of 1284/1301 (98.7%) among eligible participants (Figure).

The mean age of the participants was 35.1 years (standard deviation ± 10.2, interquartile range [IQR] 28–40; n = 1276); the median CD4 count was 337 cells/µl (IQR 199–511; n = 1114). Most participants were female (885/1280, 69.1%), 25 (2.8%) of whom were pregnant. One hundred and eleven participants (8.9%) had previously been treated for TB: 8/111 (7.2%) in the past 2 years and 103/111 (92.8%) over 2 years previously (Table 1).

IPT completion among HIV-positive adults
Of the 1284 IPT initiators, 320 (24.9%, 95% confidence interval [CI] 22.6–27.4) did not complete 6 months of therapy. Non-completion of IPT was due to LTFU (243/320, 75.9%), death (10/320, 3.1%), development of active/presumptive TB (4/320, 1.3%) and approved decision to discontinue IPT (63/320, 19.7%) (Table 2). Of the 63 participants whose IPT was discontinued, 50 (79.4%) were due to side effects, including peripheral neuropathy (12.0%), nausea/vomiting (12.0%), skin rash (46.0%) and other possible adverse reactions (30.0%). The reason for discontinuing IPT was not recorded for 13 participants.

Approximately half of this large cohort study comprised HIV-positive participants who were started on cotrimoxazole as well as a first-line ART regimen (stavudine/lamivudine/nevirapine [d4T/3TC/NVP]), which is known to have side effects that overlap with those of INH, notably peripheral neuropathy, hepatitis and nausea. IPT was generally safe and well tolerated, with only 60 (4.6%) participants reporting side effects. Eight patients developed peripheral neuropathy, all of whom had also recently been initiated on d4T-containing ART regimens. Other side effects, including skin rash, were
Table 1  Demographic and clinical characteristics of HIV-positive participants who started IPT

| Characteristic                  | (n = 1284)* | n (%)         |
|--------------------------------|-------------|---------------|
| Age, years, mean ± SD (n = 1276) | 35.1 ± 10.2 |               |
| Age group, years                |             |               |
| 16–24                          | 148 (11.6)  |               |
| 25–34                          | 544 (42.6)  |               |
| 35–49                          | 479 (37.5)  |               |
| ≥ 50                           | 105 (8.3)   |               |
| Sex                            |             |               |
| Male                           | 395 (30.9)  |               |
| Pregnant female                | 25 (2.0)    |               |
| Non-pregnant female            | 860 (67.1)  |               |
| WHO stage                      |             |               |
| Stage 1 or 2                   | 927 (76.6)  |               |
| Stage 3 or 4                   | 284 (23.4)  |               |
| CD4 count, cells/µl, median [IQR] (n = 1114) | 336.5 [199–511] |   |
| CD4 subgroup, cells/µl         |             |               |
| <100                           | 87 (7.8)    |               |
| 100–349                        | 492 (44.2)  |               |
| ≥ 350                          | 535 (48.0)  |               |
| HIV test provider†             |             |               |
| Other providers, post 2012     | 806 (63.6)  |               |
| Study, post 2012               | 424 (33.4)  |               |
| Other providers, before 2012   | 38 (3.0)    |               |
| Reported treatment for TB      |             |               |
| Never                          | 1130 (91.1) |               |
| Yes, >2 years                  | 103 (8.3)   |               |
| Yes, <2 years                  | 8 (0.6)     |               |
| ART status                     |             |               |
| d4T/3TC/NVP                    | 441 (35.0)  |               |
| Other regimen‡                 | 327 (26.0)  |               |
| ART not eligible§              | 176 (14.0)  |               |
| ART eligible, not yet started¶ | 315 (25.0)  |               |
| IPT initiation year            |             |               |
| 2012                           | 603 (47.0)  |               |
| 2013                           | 576 (44.9)  |               |
| 2014                           | 105 (8.1)   |               |
| Side effects§                  |             |               |
| Skin rash                      | 27 (2.1)    |               |
| Peripheral neuropathy          | 8 (0.6)     |               |
| Nausea/vomiting                | 7 (0.5)     |               |
| Other adverse reactions        | 18 (1.4)    |               |
| None                           | 1224 (95.4) |               |

* Excludes missing data on age (n = 8), sex (n = 94), WHO stage (n = 73), CD cell count (n = 110), HIV test provider (n = 16), reported treatment for TB (n = 43) and ART status (n = 25).
† Provider of their first HIV-positive diagnosis.
‡ Switched to other regimen due to possible adverse events due to ART regimen (d4T/3TC/NVP), such as neuropathy, hepatitis, rash, lipodystrophy, lactic acidosis or treatment failure.
§ Participants not eligible for ART at IPT initiation in accordance with Malawi national guidelines at the time of the study (eligible: WHO stage 3 or 4, or CD4 < 350 cells/µl or pregnant, or breastfeeding).
¶ Participants eligible for ART but did not start ART at IPT initiation.
# Skin rash (mild, probable), peripheral neuropathy (severe, definitely), nausea (moderate, definitely), other adverse (moderate, possibly). HIV = human immunodeficiency virus; IPT = isoniazid preventive therapy; SD = standard deviation; WHO = World Health Organization; IQR = interquartile range; TB = tuberculosis; ART = antiretroviral therapy; d4T = stavudine; 3TC = lamivudine; NVP = nevirapine.

frequent and non-severe. Grade 2 nausea and vomiting were the least observed IPT side effects. There was no case of severe hepatitis. Verbal autopsy of 10 participants who died during treatment did not suggest any relationship to IPT.

Comparing the years of IPT implementation, a sharp decrease in the proportion of participants failing to complete IPT occurred in those initiating treatment from 2012 (222/603, 36.8%) to 2013 (84/576, 14.6%) and 2014 (14/105, 13.3%). Overall, LTFU was the most common reason for non-completion of IPT in all years (Table 2).

**Risk factors for non-completion of IPT**

In univariate analysis, WHO stage 3/4, CD4 count <100 cells/µl, CD4 count 100–349 cells/µl, history of anti-tuberculosis treatment and having side effects were independently associated with non-completion of IPT; participants with WHO stage 3/4 had just over 3-fold increased odds of not completing IPT compared with those in WHO stage 1/2 (odds ratio [OR] 3.13, 95% CI 2.35–4.16). Participants with CD4 count <100 cells/µl or 100–349 cells/µl were more likely not to complete IPT than those with CD4 count > 350 cells/µl (OR 2.21, 95% CI 1.36–3.58 and OR 1.48, 95% CI 1.11–1.98, respectively). Furthermore, participants who had been treated for TB over 2 years previously were more likely not to complete IPT than those without a history of anti-tuberculosis treatment (OR 1.56, 95% CI 1.01–2.42). There was a 23-fold greater risk of non-completion of IPT among participants who experienced side effects than among those without side effects (OR 23.3, 95% CI 10.90–49.69) (Table 3).

In multivariate analysis, the following variables remained significantly associated with non-completion of IPT: WHO stage 3/4 (adjusted OR [aOR] 1.76, 95% CI 1.22–2.55, P = 0.004), CD4 count 100–349 cells/µl (aOR 1.93, 95% CI 1.10–3.38, P = 0.024) and reporting side effects (aOR 22.00, 95% CI 9.45–46.71, P < 0.001) (Table 3).

**DISCUSSION**

A quarter of the adults diagnosed as HIV-positive did not complete IPT in this prospective cohort study, which recruited participants from urban communities of Blantyre. Independent risk factors for non-completion of IPT included being in WHO stage 3 or 4, having a CD4 count of < 350 cells/µl and having side effects due to INH. Most non-completion (75.9% of 320 non-completers) was due to LTFU for unknown reasons.

The highest risk period for LTFU was immediately after confirmatory HIV testing, but before assessment for IPT eligibility (168/1725, 9.7%). The period immediately following diagnosis is known to be a high-risk period for loss to health services for other conditions, such as TB, as well as for HIV testing in routine clinics. National HIV programmes should focus on supporting newly diagnosed patients to remain in care, and they should streamline and integrate IPT eligibility assessments as far as possible. The completion rate of 75.1% reported in the present study is much higher than estimates from several
other studies,18,28,29 but lower than in two studies nested within the DarDar trial in Tanzania21,23 and a study in Zimbabwe. This finding suggests that setting-specific factors, including the configuration of joint HIV-TB services, have an important influence on completion of IPT, underscoring the importance of studies such as this one. While those aged <30 years and females have been shown to be less likely to complete IPT in previous studies in Africa,23,29 we did not find these characteristics to be associated with non-completion of IPT in the present study, which provided IPT separately from other routine HIV care, but at the primary care level.

Our data show evidence of programmatic learning and the importance of an accompanying ART regimen, with substantially lower discontinuation rates in 2014 than in 2012. This is likely due to the combination of growing prescriber confidence from familiarity with IPT and a programme switch to a better tolerated first-line ART regimen (tenofovir/lamivudine/efavirenz, TDF/3TC/EFV) from February 2014. It should be noted that the previous d4T-containing first-line ART regimen (d4T/3TC/NVP) was the most likely cause of peripheral neuropathy in patients started on both ART and IPT (as pyridoxine was provided to minimise INH-related peripheral neuropathy). However, to simplify subsequent ART management, we elected to manage these events pragmatically by discontinuing IPT and referring patients for alternative first-line ART.

Limitations of the present study included use of self-reported adherence and pill counts, which are less sensitive measures of adherence than, for example, urine drug tests or electronic Medication Event Monitoring System devices. Our completion rates could therefore have been overestimated. Other characteristics, such as marital status, education levels, employment status, religion and ethnicity, play roles in treatment adherence, as reported by other studies,28,29 and were not captured in the present study.

The main strength of our study was that potential predictors of non-completion of IPT were determined before ascertaining the outcome, thereby minimising information bias. Unrecognised deaths have comprised a substantial fraction of LTFU in other studies, and could explain the higher rates of non-completion among immunosuppressed individuals reported here. However, we think this is unlikely, as the parent study had systematic reporting of all deaths in the community with follow-up verbal autopsy. An alternative explanation could be that participants with lower CD4 counts may have been more likely to migrate out of this urban slum setting if unable to work due to ill health.

The main policy implications of our findings are to underscore the increased risk of loss to TB prevention services in the period immediately following HIV diagnosis. Our data also highlight the importance of early diagnosis of HIV and prompt ART and IPT initiation,30 as the more severely immunosuppressed HIV-positive adults were at greater risk of failing to complete IPT. A number of interventions, including automated mobile phone short message services (SMS), smart-phone applications and home visits by lay counsellors, could be considered to provide extra support to help retain high-risk individuals in their first months of HIV care.31 IPT guidelines would benefit from detailing the health messages and information needed by individuals initiating IPT to specifically address the potential side effects for patients starting both ART and IPT.

In summary, completion of 6 months of IPT among HIV-positive adults from poor urban communities in Malawi was suboptimal, but better than observed in several other primary care clinic settings. IPT was well tolerated, especially in the year after the national switch away from a d4T-containing first-line ART regimen. Interventions to further improve retention

### Table 2  Retention rates (cumulative percentage) and outcomes of patients enrolled on IPT in Blantyre, Malawi

|                      | 2012 n (%) | 2013 n (%) | 2014 n (%) | Total n (%) |
|----------------------|------------|------------|------------|-------------|
| Enrolled, n          |            |            |            |             |
| Retained after 1 month | 557 (92.4) | 528 (91.7) | 95 (90.5)  | 1180 (91.9) |
| Retained after 2 months | 471 (78.1) | 521 (90.5) | 94 (89.5)  | 1086 (84.6) |
| Retained after 3 months | 434 (72.0) | 517 (89.8) | 94 (89.5)  | 1045 (81.4) |
| Retained after 4 months | 398 (66.0) | 503 (87.3) | 92 (87.6)  | 993 (77.3)  |
| Retained after 5 months | 381 (63.2) | 492 (85.4) | 91 (86.7)  | 964 (75.1)  |
| IPT outcomes         |            |            |            |             |
| Active/presumptive TB | 1 (0.2)    | 3 (0.5)    | 0          | 4 (0.3)     |
| Died                 | 6 (1.0)    | 4 (0.7)    | 0          | 10 (0.8)    |
| Stopped              | 39 (6.5)   | 20 (3.5)   | 4 (3.8)    | 63 (4.9)    |
| Lost to follow-up    | 176 (29.1) | 57 (9.9)   | 10 (9.5)   | 243 (18.9)  |
| Completed            | 381 (63.2) | 492 (85.4) | 91 (86.7)  | 964 (75.1)  |

IPT = isoniazid preventive therapy, TB = tuberculosis.
should target the period immediately after HIV diagnosis, with support for the more immunosuppressed patients, as well as providing treatment literacy on the benefits of IPT and known side effects. Programmes offering IPT through clinics that are not fully integrated into other pre-ART and ART services should also focus on supporting patients to complete their first and second months of IPT initiation, as most patients drop out at these stages.

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References

1 Houben R M G J, Dodd P J. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLOS Med 2016; 13: e1002152.

2 World Health Organization. Global tuberculosis report, 2016. WHO/HTM/TB/2016.13. Geneva, Switzerland: WHO, 2016. 
http://apps.who.int/iris/bitstream/10665/250441/1/ WHO89241565394-eng.pdf?ua=1 Accessed November 2017.
1. Al-Darraj H A A, Kamarulzaman A, Altice F L. Isoniazid preventive therapy in correctional facilities: a systematic review [Review]. Int J Tuberc Lung Dis 2012; 16: 871–879.

2. Takarinda K C, Choto R C, Harries A D, Mutasa-Apollo T, Chakanyuka-Musanhu C. Routine implementation of isoniazid preventive therapy in HIV-infected patients in seven pilot sites in Zimbabwe. Public Health Action 2017; 7: 55–60.

3. Corbett E L, Marston B, Churchyard G J, De Cock K M. Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. Lancet 2006; 367: 926–937.

4. Lawn S D, Wood R, Cock K M D, Kranzer K, Lewis J J, Churchyard G J. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. Lancet Infect Dis 2010; 10: 489–498.

5. Ayele H T, Mourik M S, Debray T P, Bonten M J. Isoniazid prophylactic therapy for the prevention of tuberculosis in HIV infected adults: a systematic review and meta-analysis of randomized trials. PLOS ONE 2015; 10: e0142290.

6. Samandari T, Agizew T B, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet 2011; 377: 1588–1598.

7. Durouvi B, Saraceni V, Moulton L H, et al. Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial. Lancet Infect Dis 2013; 13: 852–858.

8. Kufa T, Chihota V N, Charalambous S, Churchyard G J. Isoniazid preventive therapy use among patients on antiretroviral therapy: a missed opportunity [Short communication]. Int J Tuberc Lung Dis 2014; 18: 312–314.

9. Rangaka M X, Wilkinson R J, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet 2014; 384: 682–690.

10. World Health Organization. Recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB and HIV-prevalence settings: 2015 update. WHO/HTM/TB/2015.15 and WHO/HIV/2015.13. Geneva, Switzerland: WHO, 2015. http://www.who.int/tb/publications/2015_ipt_update/en/ Accessed November 2017.

11. Getahun H, Kittikrasik W, Heilig C M, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. PLOS Med 2011; 8: e1000391.

12. Person A K, Sterling T R. Treatment of latent tuberculosis infection in HIV: shorter or longer? Curr HIV/AIDS Rep 2012; 9: 259–266.

13. World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, Switzerland: WHO, 2011. http://www.who.int/tb/challenges/hiv/ICP_IPTguidelines/en/ Accessed November 2017.

14. Lewis J J, Fielding K L, Grant A D, et al. Eligibility for isoniazid preventive therapy in South African gold mines. PLOS ONE 2013; 8: e81376.
CONTEXTE : En dépit de l’expansion mondiale des services de prise en charge de l’infection par le virus de l’immunodéficience humaine (VIH), assez peu de pays ont mis en œuvre le traitement préventif par isoniazide (IPT) en routine. Parmi d’autres préoccupations programmatiques, l’achèvement de l’IPT tend à être faible, surtout quand il n’est pas totalement intégré dans les centres de traitement du VIH.

OBJECTIF : Estimer le niveau de non-achèvement des 6 mois d’IPT et ses facteurs de prédiction parmi des adultes âgés de ≥16 ans positifs au VIH.

SCHÉMA : Une étude prospective de cohorte au sein d’un essai randomisé en grappes de prévention de la tuberculose (TB) a été réalisée entre février 2012 et juin 2014. Un IPT de 6 mois a été fourni avec de la pyridoxine dans les centres de l’étude. Le non achèvement a été défini comme une perte de vue, un décès, une TB active/présumée ou un arrêt de l’IPT pour n’importe quelle autre raison. Une régression logistique à effets aléatoires a été utilisée pour déterminer les facteurs de prédiction de non achèvement.

RÉSULTATS : Sur 1284 adultes positifs au VIH mis sous IPT, 885/1280 (69,1%) étaient des femmes et le CD4 médian a été de 337 cellules/µl (intervalle interquartile 199–511). Des 1284 adultes positifs au VIH, 320 (24,9%) n’ont pas achevé l’IPT. Après contrôle du statut du traitement antirétroviral, de l’année de mise en route de l’IPT, de l’âge et du sexe, le non achèvement de l’IPT a été associé au stade 3–4 de l’Organisation Mondiale de la Santé (OR ajusté [ORa] 1,76 ; IC95% 1,22–2,55), le nombre de CD4 100–349 cellules/µl (ORa 1,93 ; IC95% 1,10–3,38) et tout effet secondaire rapporté (ORa 22,00 ; IC95% 9,45–46,71).

CONCLUSION : L’achèvement de l’IPT a été sous-optimal. Les interventions visant à améliorer la rétention devraient cibler les adultes immunodéprimés positifs au VIH et aborder le problème des effets secondaires.

RESUMEN

MARCO DE REFERENCIA: Pese a la ampliaciòn mundial de escala de los servicios relacionados con la infección por el virus de la inmunodeficiencia humana (VIH), relativamente pocos países han introducido el tratamiento preventivo con isoniazida (IPT) en la práctica corriente. Entre otras dificultades programáticas, se observa una baja tasa de completión del IPT, sobre todo cuando no se encuentra plenamente integrado en los consultorios de atención de la infección por el VIH.

OBJETIVO: Calcular la tasa de tratamientos incompletos con un esquema de TPI de 6 meses y definir los factores asociados, en adultos a partir de los 16 años de edad, positivos frente al VIH.

MÉTODO: Se llevó a cabo un estudio de cohortes prospectivo, anidado en un ensayo clínico aleatorizado por conglomerados sobre la prevención de la tuberculosis (TB), de febrero del 2012 a junio del 2014. El IPT con piridoxina se suministró durante 6 meses en los consultorios del estudio. La falta de compleción del tratamiento se definió como pérdida durante el seguimiento, muerte, TB activa confirmada o su presunción o interrupción del IPT por cualquier otra razón. Con un modelo de regresión logística de efectos aleatorios se determinaron los factores pronósticos de un tratamiento incompleto.

RESULTADOS: Se inició el IPT en 1284 adultos positivos frente al VIH; 885 de 1280 eran de sexo femenino (69,1%) y la mediana de la cifra de linfocitos CD4 fue 337 células/µl (amplitud intercuartílica 199–511). No completaron el IPT 320 de los 1284 pacientes (24,9%). Tras ajustar con respecto a la situación frente al tratamiento antirretroviral, el año de iniciación del IPT, la edad y el sexo, la falta de compleción del tratamiento se asoció con el estado 3 o 4 de la enfermedad según la clasificación de la Organización Mundial de la Salud (OR ajustado [ORa] 1,76; IC95% 1,22–2,55), la cifra de linfocitos CD4 de 100-349 células/µl (ORa 1,93; IC95% 1,10–3,38) y la notificación de algún efecto secundario (ORa 22,00; IC95% 9,45–46,71).

CONCLUSIÓN: La tasa de compleción del IPT fue deficiente. Las intervenciones encaminadas a mejorar la retención en la atención se deben dirigir a los adultos positivos frente al VIH con inmunodepresión y deben abordar los efectos secundarios.