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Isoniazid-associated pellagra during mass scale-up of tuberculosis preventive therapy: a case-control study

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Declaration of interests

We declare no competing interests.

Data sharing

The data from this study are owned by the Malawi Ministry of Health and can be released only after the Ministry has provided their written approval for additional analyses. The data are available upon request. To request data, please contact the Kamuzu University of Health Sciences Research Ethics Committee at comrec@medcol.mw.

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Summary

Background—Pellagra is caused by niacin (vitamin B3) deficiency and patients with pellagra present with a characteristic rash. Isoniazid disrupts intracellular niacin synthesis and might induce

niacin deficiency. In 2017, Malawi scaled up continuous isoniazid preventive treatment (IPT) for tuberculosis prevention among people living with HIV. In addition, an under-diversified diet based on subsistence maize, as is commonly the case in Malawi, is a risk factor for pellagra. We aimed to investigate whether large-scale isoniazid exposure in Malawi contributed to the cumulative risk for pellagra in a nutritionally vulnerable population.

Methods—We did a matched case-control study to evaluate the association between daily, continuous isoniazid exposure and pellagra. We matched sequentially enrolled patients with pellagra each with four control participants by sex and age from referral dermatology centres in three IPT scale-up districts in Malawi (Lilongwe, Blantyre, and Zomba) to evaluate isoniazid as a risk for pellagra using multivariable conditional logistic regression. We established a community clinic referral system surrounding the dermatology clinic in each district to enhance case-finding and included all patients with pellagra, regardless of referral status. The primary outcome was dermatologist-diagnosed pellagra. We calculated the interval between isoniazid initiation and rash onset and assessed 30-day clinical outcomes after multi-B vitamin treatment containing 300 mg nicotinamide daily.

Findings—Between Feb 5 and Aug 9, 2019, we enrolled 197 patients with pellagra and 781 matched controls. Isoniazid exposure was associated with an increased risk of pellagra (adjusted odds ratio 42·6 [95% CI 13·3–136·6]). Significant covariates included HIV infection, referral status, food insecurity, underweight, excess alcohol consumption, and, among women, lactation. The median time from isoniazid initiation to rash onset was shorter during the season of food scarcity (5 months [IQR 3–7]) compared with the harvest season (9 months [8–11]; hazard ratio 7·2 [95% CI 3·2–16·2], log-rank p<0·0001). Those with isoniazid-associated pellagra who discontinued isoniazid and adhered to multi-B vitamin treatment showed 30-day clinical improvement.

Interpretation—Continuous IPT scale-up and the annual period of food scarcity both increased the risk of pellagra in Malawi. Use of shorter rifamycin-based regimens for tuberculosis prevention and food fortification in populations with undernutrition might reduce this risk. Niacin-containing multi-B vitamin co-administration with isoniazid as pellagra prevention is worth exploring further.

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Introduction

Pellagra is caused by niacin (vitamin B3) deficiency, presents with a characteristic rash, and is diagnosed clinically.[1] Advanced pellagra that is untreated can cause death. Unfortified maize is low in bioavailable niacin and Malawians are high maize consumers.[2] In Malawi, 85% of maize is locally processed (ie, where it is produced) and rarely fortified; less than half of the centrally processed maize is fortified.[3] An under-diversified diet based on subsistence maize is a risk factor for pellagra.[4]

Isoniazid prevents tuberculosis and deaths in people living with HIV.[5] However, isoniazid has been implicated as a secondary cause of pellagra by inhibiting niacin production from the amino acid tryptophan.[6] HIV infection also disrupts tryptophan catabolism and can

lower intracellular niacin.[7] Despite decades of efforts by international agencies and national programmes to distribute tuberculosis preventive treatment among people living with HIV, large-scale implementation had been scarce until recently.[8] In 2018, the UN General Assembly declared a goal to give tuberculosis preventive treatment to 30 million people (including 6 million people living with HIV) by 2022.[9] The US President's Emergency Plan for AIDS Relief (PEPFAR) also set an ambitious target of providing tuberculosis preventive treatment to 13 million people living with HIV by 2022.[10] The Malawi Ministry of Health revised national guidelines to provide daily, continuous isoniazid with vitamin B6 (pyridoxine) for people living with HIV in the highest burden districts facing generalised epidemics of HIV and tuberculosis.[11] From Aug 1 to Oct 31, 2017, more than 250 000 people living with HIV across five districts in Malawi initiated isoniazid preventive treatment (IPT; adult dose: 300 mg isoniazid plus 25 mg vitamin B6 [pyridoxine]).[12] Within 3 months, which coincided with the annual food-scarce season, clinicians noticed an increased incidence of pellagra among people living with HIV and taking IPT. We hypothesised that large-scale isoniazid exposure in Malawi contributed to the cumulative risk for pellagra in a nutritionally vulnerable population.

Methods

Study design and participants

We did a matched case-control study to evaluate the association between daily, continuous isoniazid exposure and pellagra, as described in detail previously.[13] We sequentially recruited all patients with pellagra from purposively selected referral dermatology centres in three IPT scale-up districts in Malawi (Lilongwe, Blantyre, and Zomba). We randomly selected three high-volume peripheral health centres surrounding each dermatology centre to enhance pellagra case-finding and referrals.[13] We included all patients with pellagra confirmed by a dermatologist, whether by a walk-in appointment or referral to the dermatology centre.

To each patient with pellagra, we matched four control participants by sex and age strata (ie, ≤14 years, 15–24 years, 25–34 years, 35–44 years, 45–54 years, 55–64 years, and ≥65 years). We selected control participants from the same dermatology centre within the same season and without considering HIV or tuberculosis status, or isoniazid exposure. Thus, participants could have been exposed to isoniazid as part of multidrug treatment for tuberculosis or as IPT for people living with HIV. We excluded controls who had diarrhoea or altered mental status because these might be features of pellagra, and those with dermatoses that highly resemble pellagra. The Kamuzu University of Health Sciences Research and Ethics Committee (P.10/18/2512), Centers for Disease Control and Prevention (CDC) Human Research Protection Office (7173), and Advarra Institutional Review Board (30840) approved the study. All participants gave written informed consent.

Procedures

We confirmed the current HIV status for every participant. If the participant's documented status was not known or not up to date per national guidelines, we recommended immediate, no-cost HIV testing within the recruitment facility, and offered same-day linkage to HIV

care for new diagnoses. We also verified concurrent antiretroviral therapy (ART), defined as receiving ART services at the time of enrolment, via participants' health records.

We measured food security using the Household Food Insecurity Access Scale measurement tool.[14] During the annual food-scarce season (ie, approximately November to March every year), many subsistence families must skip meals, substitute foods with lower nutrition, and limit food diversity. Trained study nurses measured weight (kg), height (cm), and mid-upper-arm circumference (MUAC; cm) for all particpants.[13] A body-mass index of less than 18·5 kg/m^2 classified adult men and non-pregnant adult women as underweight; for pregnant women, a MUAC of less than 23 cm defined underweight. Because no validated tool for dietary niacin consumption exists, we estimated recent dietary niacin intake using a 7-day food frequency questionnaire of 16 niacin-rich foods commonly available in Malawi, and we calculated a niacin diversity score based on intake and niacin content.[13] We defined excessive alcohol consumption as either drinking for at least 10 of the past 14 days, regardless of the number of drinks consumed per day, or feeling drunk at least 3 times in the past 14 days.[13]

We dispensed a 30-day supply of multi-B vitamins (containing a daily dose of 300 mg of nicotinamide) to participants with pellagra, whether isoniazid-associated or not, for self-administration. The daily multi-B vitamin also contained thiamine (30 mg), riboflavin (30 mg), pyridoxine (9 mg), cobalamine (45 μg), calcium panthenate (150 mg), folic acid (4·5 mg), biotin (300 μg), and ascorbic acid (450 mg). We also instructed participants to discontinue isoniazid if they were taking the treatment, and scheduled their return appointment at 30 days.

We requested urine from all people living with HIV and from those HIV-negative participants who reported isoniazid exposure, and analysed them using IsoScreen (GFC Diagnostics, Oxfordshire, UK) to detect isoniazid metabolites. We combined positive and indeterminate IsoScreen readings to a single response representing recent isoniazid ingestion. To analyse the niacin urine metabolites 1-methylnicotinamide (1-MN) and l-methyl-2-pyridone-5-carboxamide (2-PYR), we collected urine from the initial 125 sequentially enrolled patients with pellagra and their first matched control. To optimise statistical comparisons, we aimed to collect at least 20 specimens per subgroup (ie, HIV-negative people, people living with HIV not receiving ART [each with and without isoniazid exposure], and people living with HIV receiving both ART and isoniazid). For categories not meeting the quota through case-control enrolment, we purposively recruited additional urine donors to compare niacin status across these strata. We did not include data from these extra urine donors in the epidemiological comparison of patients with controls.[13] Our final urinalysis sample included 119 confirmed patients with pellagra, 139 control participants, and 40 extra urine donors (appendix p 10). We quantified 1-MN and 2-PYR following published methods.[15]

Outcomes

The primary outcome was dermatologist-diagnosed pellagra. Patients with pellagra needed to have a rash on sun-exposed areas (ie, face, feet, hands, forearms, or legs) or a distinctive neck or chest plaque (Casal necklace) without an alternative cause explaining the rash.[1]

Secondary outcomes were the time from isoniazid initiation to rash onset (latency), objective dermatologist assessment of rash resolution, subjective symptomatic improvement with multi-B vitamin treatment, and urine concentration of niacin metabolites. We defined low niacin status through urine sampling as 2-PYR/1-MN <1·0, and deficiency as 2-PYR/1-MN <0·5 on the basis of WHO guidelines.[1]

Statistical analysis

We used Stata 17 and SAS 9.4 for the analyses. To detect an odds ratio (OR) of at least 2·0 with 90% power, assuming isoniazid exposure as low as 12% among four control participants per case, we determined the sample size to be 197 patients with pellagra and 788 control participants.[13] We applied two methods for defining isoniazid exposure. For multivariable modelling, we used self-reported isoniazid exposure within 2 months of enrolment to preserve the potentially longer-term effects of daily isoniazid on pellagra risk. To assess niacin status, we stratified isoniazid exposure using urine metabolite detection via IsoScreen. We chose this methodology because IsoScreen detection has a closer, more objective temporal relationship with urine isoniazid metabolite detection relative to ingestion time (~24 h) than would be possible through participant recall and doing so better represents adherence with daily isoniazid treatment. In multivariable modelling, we also analysed documented HIV and underweight status, food-security score, alcohol consumption, dietary diversity, maize fortification, receipt of household food aid during the previous year, regular source of income, patient referral status (walk-in *vs* referral), self-reported pregnancy and lactation among women, concurrent vitamin B6 supplementation and tuberculosis treatment among isoniazid-exposed participants, and duration of HIV infection and concurrent ART among HIV-positive individuals. For missing values, we used multiple imputation with conditionally specified chained equations.[16] We generated 25 completed datasets from multiple imputations and combined results across imputations using Rubin's rules.[17]

We estimated pellagra risk using conditional logistic regression and we assessed variables for collinearity, notably between isoniazid exposure and HIV. We calculated descriptive summaries for latency, symptom improvement, and niacin status using the 2-PYR/1-MN fraction.[1] Because some of the specimens were purposively sampled, we compared differences in median ratios between unmatched groups with the Wilcoxon two-sample *t* test approximation. Among isoniazid-associated patients with pellagra only, we used a Kaplan-Meier survival analysis to compare latency according to isoniazid initiation during the annual period of increased food scarcity (defined as November to March) against isoniazid initiation in all other months. As with the urine niacin metabolite analyses, we did not compare matched case-control groups in the survival analysis. Because people living with HIV in the study population were eligible for continuous IPT from Sept 1, 2017, and study enrolment occurred up to Aug 9, 2019, some people living with HIV could have been exposed to continuous isoniazid for up to 24 months.

Role of the funding source

This project was supported by PEPFAR through the CDC under the terms of project 7173. The CDC was involved with study design; data collection, analysis, and interpretation; writing of the report; and the decision to submit for publication.

Results

Between Feb 5 and Aug 9, 2019, we enrolled 197 patients with pellagra and 781 matched control participants. 71 (38%) of 188 evaluated study-sponsored referrals had dermatologist-confirmed pellagra (figure 1). An additional 129 people with confirmed pellagra were reported to enrolment sites through routine mechanisms. We enrolled 197 (99%) of 200 eligible people with pellagra; 195 (99%) of 197 remained engaged through the 30-day clinical re-assessment. Control participants largely presented to care with infections and parasitic infestations (314 [40%] of 781), inflammatory disorders (186 [24%]), and mild-to-moderate eczema (178 [23%]). Patients with pellagra were aged 13–76 years (mean 36·1 [SD 10·4]) and were largely women of childbearing age: 156 (79%) of 197 were female and aged 15–45 years (table 1). Notably, 39 (20%) of 197 patients with pellagra were lactating women with HIV, whereas there were only five pregnant women with pellagra. Control participants were aged 12–77 years (mean 36·1 [SD 10·6]). Women comprised 165 (84%) of 197 patients with pellagra and 653 (84%) of 781 control participants. All participants were Black African. A higher proportion of patients with pellagra reported isoniazid exposure within 2 months (159 [81%] of 197) compared to controls (91 [12%] of 781), largely for tuberculosis prevention. A higher proportion of patients with pellagra also had an HIV infection (171 [87%]) compared to controls (170 [22%]; table 1). Moderate or severe food insecurity was common among both patients with pellagra and controls and nearly all households consumed unfortified maize. The median time from rash onset to pellagra diagnosis was 3 weeks (IQR 2–6, range <1–31). At any time before enrolment, 22 (22%) of 99 participants discontinued isoniazid due to rash. Other reasons for pre-enrolment discontinuation of isoniazid included nausea, dyspepsia, or vomiting (13 [13%] of 99); peripheral numbness or tingling (nine [9%]); dizziness (eight [8%]); body aches (four [4%]); palpitations (four [4%]); running out of medicine (four [4%]); and suspected tuberculosis disease (one [1%]). Of the 43 individuals who discontinued isoniazid at least 2 months before enrolment, 22 (51%) implicated a rash: seven (78%) of nine patients with pellagra and 15 (44%) of 34 controls. These 43 individuals were not counted as isoniazid-exposed.

Pellagra was associated with self-reported isoniazid exposure within 2 months of rash (adjusted OR 42·6 [95% CI 13·3–136·6]) and HIV infection (3·2 [1·0–9·7]), as well as moderate and severe food insecurity, underweight, excessive alcohol consumption, and being referred to the clinic (table 2). In a subgroup analysis of 818 women, pellagra was also weakly associated with lactating (3·2 [1·0–10·5]; appendix pp 6–8). Parity and regular income did not predict pellagra upon multivariate adjustment. In a subgroup analysis of 257 isoniazid-exposed patients, pellagra was weakly associated with the duration (in months) of isoniazid exposure (1·1 [1·0–1·3]), and vitamin B6 supplementation showed mild evidence of a protective effect (0·2 [0·1–1·0]; appendix pp 6–8). Isoniazid exposure was collinear with HIV (Phi=0·54). ART use and HIV duration were not associated with pellagra in a subgroup analysis of 378 HIV-positive participants (appendix pp 6–8).

The interval between isoniazid initiation and onset of rash varied from less than 1 month to 24 months. The median interval differed between those who started on isoniazid during the food-scarce season (5 months [IQR 3–7]) and those who started during all other months (9

months [8–11]; log-rank p<0·0001; figure 2). The corresponding hazard ratio was 7·2 (95% CI 3·2–16·2). Referral bias did not explain this difference (appendix p 11).

We identified no deaths attributable to pellagra. Prompt cessation of isoniazid and daily multi-B vitamin adherence was high among participants with isoniazid-associated pellagra: 147 (94%) of 156 stopped isoniazid immediately upon diagnosis, and most (136 [87%] of 156) reported missing no doses. At the 30-day reassessment, those who promptly discontinued isoniazid upon diagnosis had a higher frequency of complete rash resolution (77 [52%] of 147) compared with those whose isoniazid discontinuation was delayed or never done (one [11%] of eight; p=0·030; appendix p 5). A large proportion of case patients reported improvement in other symptoms at 30 days (appendix p 5).

Niacin metabolite results were available for 258 participants (119 patients with pellagra and 139 controls; appendix pp 9–10). The 2-PYR/1-MN fraction was lower in patients with pellagra (median 2·28 [IQR 1·14–4·04]) than in control participants (2·72 [1·73–4·09]; p=0·040), and low niacin status was twice as common in patients with pellagra (23 [19%] of 119) than in controls (13 [9%] of 139). The 82 participants with detectable isoniazid metabolites in urine had lower 2-PYR/1-MN fractions (2·19 [1·05–3·56]) than did the 87 without isoniazid metabolites (2·96 [1·75–5·19]; p=0·010; appendix p 12). The ratio was lowest for people with detectable isoniazid metabolites and pellagra (1·85 [0·94–3·26]; appendix p 12). Median metabolite ratios did not differ significantly by HIV status (appendix p 12). All but two patients with pellagra exposed to isoniazid also had HIV infection; thus, the ratio for combined isoniazid and HIV exposures among patients with pellagra resembled that for isoniazid alone (appendix p 12). The trend was lower for 28 lactating women (2·34 [1·14–3·32]) compared with 175 non-lactating women (2·58 [1·43–4·12]; p=0·23). The appendix (p 13) shows additional niacin metabolite analyses in relation to isoniazid, HIV, tuberculosis disease, vitamin B6 co-administration, and pellagra.

Discussion

This is the first epidemiological risk analysis of isoniazid and pellagra that controls for important cofactors. Isoniazid use contributed to pellagra occurrence during mass scale-up of continuous IPT in 2017, and the development of isoniazid-associated pellagra accelerated during the annual season of food scarcity. Pellagra is a multifactorial disease rooted in poverty and undernutrition in Malawi, with various contributing sociobiological pathways. These pathways include gross socioeconomic inequities, reliance on maize as an energy-rich but niacin-poor staple, and interaction with epidemic infectious diseases, which together create a situation that warrants the mass distribution of isoniazid to prevent tuberculosis among people living with HIV. The COVID-19 pandemic and climate change are likely to exacerbate the contributions of these pathways to pellagra incidence.[18–20]

The durable adjusted ORs for isoniazid exposure probably approximate the relative risk in this study population, as pellagra was rare (ie, probably a few hundred pellagra cases among more than 300 000 people living with HIV starting IPT).[21] This epidemiological association is supported by a corollary decrease in urine niacin metabolites for participants taking isoniazid. Although pellagra can have grave consequences, most cases of isoniazid-

associated pellagra in this study population were mild, typically detected within a few weeks of rash onset, and improved with isoniazid cessation and treatment.

Isoniazid-associated pellagra has not been previously described at scale in the medical literature. Despite modest progress over the years,[22] large-scale isoniazid preventive treatment among people living with HIV in sub-Saharan Africa is fairly recent.[23] In 2017, more than 250 000 people living with HIV initiated IPT in five districts, whereas less than 16 000 cases of tuberculosis disease were reported throughout Malawi in 2018.[24] These individuals with tuberculosis disease constituted the population eligible for isoniazid treatment before the scale-up of IPT. The geographically confined scale-up of continuous IPT probably aided recognition of the initial cluster.

The role of host–pathogen interactions and host population genetics in isoniazid-induced pellagra merit consideration. African populations show focal geographical heterogeneity of *NAT2*, which encodes the enzyme that kinetically regulates hepatic catabolism of isoniazid.[25] Slow NAT2 acetylation, associated with agrarian societies[25] and potentially climatic zone and biome,[26] increases the risk for isoniazid-induced hepatotoxicity[27] and might similarly increase pellagra risk.[28]

Mycobacterium tuberculosis activates the rate-limiting enzyme in the kynurenine pathway, indoleamine 2, 3-dioxygenase (IDO), in macrophages,[29] a cascade for which pyridoxine is an essential cofactor.[30] IDO activation might be part of an adaptive immune escape mechanism, and it also potentiates intracellular niacin production that is potentially bioavailable to host cells. Unlike the human host, *M tuberculosis* can also synthesise tryptophan, an input for niacin synthesis.[31] Thus, metabolically active *M tuberculosis*, as in tuberculosis disease, could theoretically attenuate the pellagra risk from isoniazid. However, isoniazid used for empirical prevention in people living with HIV who might not have *M tuberculosis* infection or who have latent, less metabolically active *M tuberculosis* infection, could plausibly have a different biological effect. These observations could inform why isoniazid-associated pellagra has not been more widely observed in the treatment of tuberculosis disease.

Others have shown that HIV also activates IDO;[7] the extent of tryptophan depletion (and thus reduced niacin production) directly correlates with immune suppression.[32] Virtually all people living with HIV in this study were taking ART, which partially reverses the activation of IDO by HIV[33] and might have attenuated the risk association for HIV in this study. With HIV in the model, we rendered isoniazid conditionally independent of HIV status. However, with so few people living with HIV in the study not having been exposed to isoniazid, the resulting collinearity, and the absence of any difference in urine niacin metabolite concentrations, our interpretation of the independent epidemiological association between HIV status and pellagra is limited. The possible contribution of HIV to pellagra nonetheless merits further study.

Lactation was a significant cofactor for pellagra in women in our model. Human reproduction diverts nutrients to the offspring, and higher niacin intake is recommended for pregnant and lactating women.[34] In our study, however, pregnancy was uncommon among

women with pellagra and it was not a significant risk for pellagra, perhaps because similar activation of IDO occurs in the placenta during normal pregnancy to prevent allogeneic rejection, which might affect maternal niacin status.[35] Finally, excessive alcohol use was associated with pellagra; per Malawi Ministry of Health guidelines, people living with HIV with excessive alcohol use should not be offered IPT.

Shorter rifamycin-based tuberculosis prevention regimens might help to avoid isoniazid-associated pellagra in at-risk populations. They are as effective and safer than longer isoniazid-only regimens and WHO endorses them for tuberculosis prevention in people living with HIV.[36] Since this investigation, Malawi has transitioned from continuous IPT after careful consideration of benefits versus toxicities in comparison with alternatives.[37] Nonetheless, IPT-associated pellagra among people living with HIV in similar settings has emerged in case reports in which continuous IPT was not used, highlighting the need for vigilance with shorter durations of isoniazid use.[38–40] Our results might be generalisable to other regions with similar nutrition profiles; eastern Africa, including Malawi, has high levels of undernutrition.[41] Study strengths include substantiation of niacin status and isoniazid exposure using urine metabolites assays, use of standardised case definitions and expert dermatological confirmation, use of peripheral health centre referrals to reduce case selection bias, and correlation of clinical improvement at 30 days. We also acknowledge its limitations. Controlling for many covariates resulted in imprecise risk estimates and we enrolled too few people living with HIV without isoniazid exposure to truly assess the independent contribution of HIV. Additionally, 22 participants discontinued isoniazid before study enrolment due to rash and were therefore not counted as exposed to isoniazid. Some might have been pellagrous rashes. Because this reason for discontinuation occurred more frequently among patients with pellagra, our model might underestimate isoniazid risk. The higher prevalence of HIV in our control group (22%) compared with the target population (11–17%)[42] might be another way in which we underestimated isoniazid risk. Despite having other markers of undernutrition, only one in five patients with pellagra had low niacin status according to standard cutoffs for defining dietary niacin deficiency, suggesting more sensitive biomarkers of isoniazid-associated pellagra are needed. Finally, we were unable to measure NAT2 acetylation status and biomarkers of HIV disease severity.

People with isoniazid-associated pellagra, although a rare condition, benefited from simple interventions, including prompt discontinuation of isoniazid and completion of a 30-day course of multi-B vitamins. Isoniazid retains a critical, lifesaving role in preventing and treating tuberculosis. As with other potential adverse effects, a risk of pellagra ought not to preclude people living with HIV from the benefits of isoniazid in tuberculosis prevention. Rather, programmes might wish to enhance patient education and pharmaco-vigilance. Currently, some national guidelines call for the co-administration of vitamin B6, a cofactor in the kynurenine pathway, with IPT to prevent neuropathy. Co-administration of vitamin B6 showed a modest protective effect in this study. Niacin-containing multi-B vitamin co-administration with isoniazid as pellagra prevention is worth exploring. Finally, addressing structural inequities and implementing innovative population-level fortification strategies in under-nourished populations remain urgent, still unfulfilled public health solutions. In their absence, targeted food supplementation and fortification efforts for people living with

HIV starting isoniazid-containing regimens, particularly people living with HIV facing food insecurity and lactating women, might prevent pellagra.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

Until recently, isoniazid has been used predominantly for the treatment of tuberculosis disease in regions with high levels of undernutrition, such as Malawi. International agencies and national health programmes have begun the mass scale-up of isoniazid use for the preventive treatment of tuberculosis for people living with HIV. Isoniazid was first implicated as a rare secondary cause of pellagra, a potentially lethal disease of niacin deficiency, shortly after its introduction as an effective treatment for tuberculosis in 1952. We searched PubMed for relevant studies published in English between Jan 1, 1952, and June 10, 2021, using the MeSH terms ("isoniazid" AND "pellagra"), and we identified 49 search results. Of these, 32 peer-reviewed publications contained case reports or case series of 51 patients identified with presumed isoniazid-associated pellagra. Most of these reports were about individuals taking isoniazid to treat tuberculosis, and many of these individuals had other risk factors for pellagra, such as excessive alcohol consumption or malabsorption. WHO produced a comprehensive technical document on the subject of pellagra, *Pellagra and its Prevention and Control in Major Emergencies*, in 2000. We did a second PubMed search of modern pellagra outbreak reports published in English from Jan 1, 1990, to June 10, 2021, using the MeSH terms ("pellagra" AND "disease outbreak") or with the title containing ("pellagra" AND "outbreak"), which resulted in 15 search results. Of these, we found seven publications reporting on five unique outbreaks, all in sub-Saharan Africa: four related to humanitarian crises of war or natural disaster, and the fifth was associated with drought in Malawi. We found no reports of medication-induced pellagra outbreaks. To date, no study has evaluated the epidemiological association between isoniazid and pellagra while controlling for other possible causes of pellagra.

Added value of this study

Isoniazid given as empirical, continuous prevention for tuberculosis has a robust, independent association with the development of pellagra in people living with HIV. People living with HIV with additional stressors (eg, who are lactating, underweight, or food insecure) appear to be at highest risk. The effect of isoniazid on the population-level risk for pellagra was amplified during periods of food scarcity, and pellagra developed in as little as a few weeks from the start of isoniazid treatment in these circumstances. Cessation of isoniazid and treatment with multi-B vitamins for 30 days largely resolved the rash and symptoms of pellagra in affected people living with HIV.

Implications of all the available evidence

Pellagra is a potentially lethal health condition and the confluence of structural factors (ie, poverty, undernutrition, and epidemic infectious diseases such as tuberculosis and HIV) leads to increased underlying pellagra risk in a population. Additional risks, such as iatrogenic induction of pellagra with isoniazid, must be avoided. People with pellagra present with a stigmatising rash, and the occurrence of pellagra as a side-effect of isoniazid could further hinder the lifesaving use of isoniazid for tuberculosis prevention. In addition to improved patient counselling and pharmacovigilance, simple

interventions for at-risk populations receiving isoniazid preventive treatment are needed. These interventions could include coadministration of multi-B vitamins with isoniazid rather than vitamin B6 alone, without substantial additional cost. Use of short-course, rifamycin-based regimens for tuberculosis prevention might help to avoid some of the unintended effects of lengthier isoniazid treatments. These preferred shorter regimens are likely to contain isoniazid and might still pose a pellagra risk in similar settings. Ultimately, improved nutritional status is needed, such as through innovative population-level food fortification strategies and reducing economic inequities. Studies to define the effectiveness of pellagra prevention strategies, particularly in the setting of short-term isoniazid use, will be beneficial.

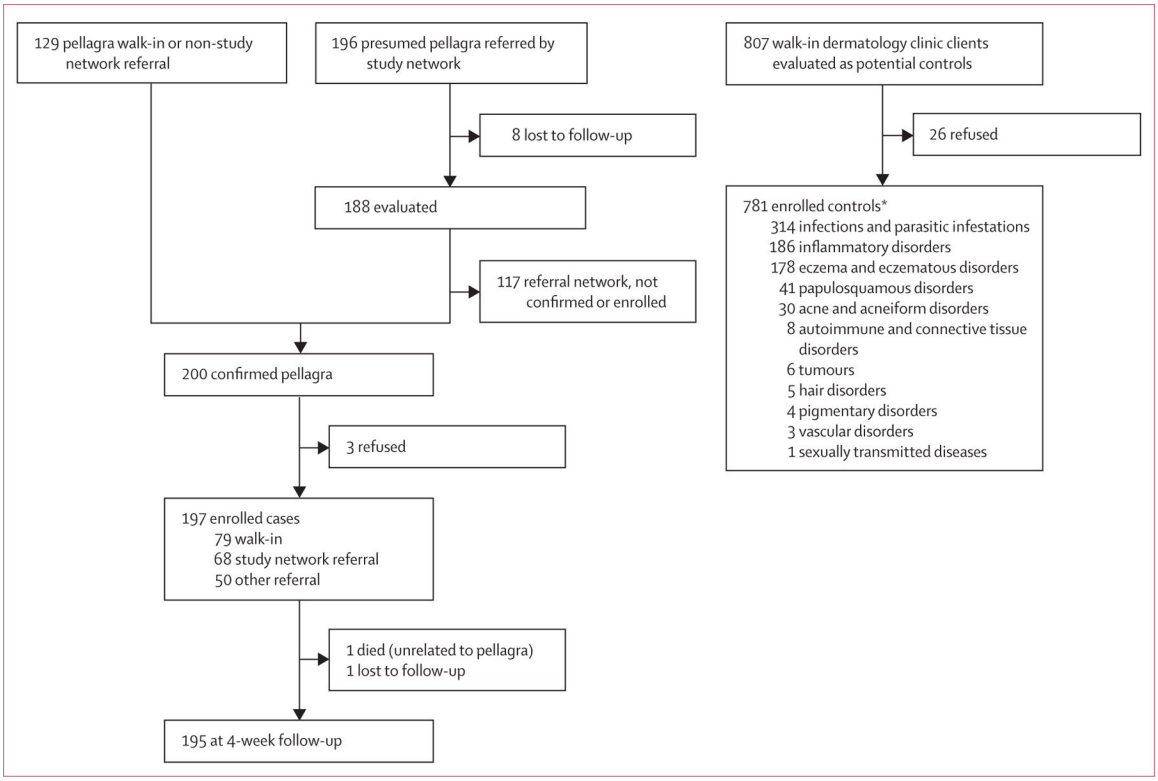

Figure 1: Study profile

*Five control participants had two diagnoses each.

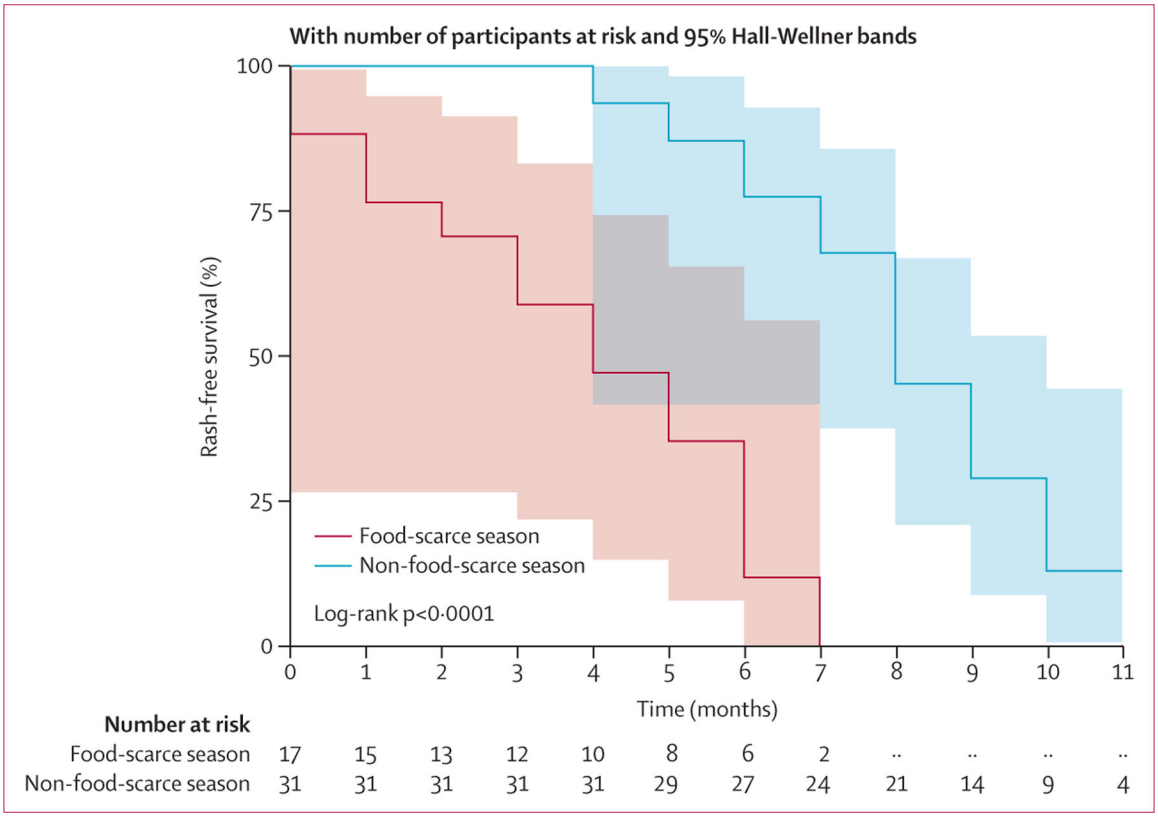

Figure 2: Isoniazid initiation to pellagrous rash onset for patients with isoniazid-associated pellagra

Kaplan-Meier curves for interval from isoniazid initiation to pellagrous rash onset among 48 patients with isoniazid-associated pellagra by initiation during the food-scarce season (red) or not (blue) in Malawi. 95% Hall-Wellner confidence bands are shown. The hazard ratio for isoniazid initiation during the food-scarce season was 7·2 (3·2–16·2). The food-scarce season is defined as November, December, January, February, and March. This analysis does not represent matched cases and controls. It was limited to 48 patients with isoniazid-associated pellagra who initiated isoniazid within 12 months of study enrolment. The estimated isoniazid start date and rash onset date was known for all 48 people with isoniazid-associated pellagra starting isoniazid within 12 months of study enrolment; therefore, no latency values were censored.

Table 1:

Enrolment characteristics of people with pellagra and age-matched and sex-matched controls presenting to three dermatology clinics

	Patients with pellagra (n=197)	Healthy controls (n=781)	p value
Age*	36·1 (10·4)	36·1 (10·6)	0·97
Sex			
Male	32 (16%)	128 (16%)	0·97
Female	165 (84%)	653 (84%)	··
Lactating women			
Yes	43/165 (26%)	61/653 (9%)	<0·0001
Pregnant women			
Yes	5/163 (3%)	17/653 (3%)	0·79
Missing	2 (1%)	0	··
Race or ethnicity			
Black African	197 (100%)	781 (100%)	1·0
Isoniazid use in past 2 months			
Yes	159 (81%)	91 (12%)	<0·0001
Missing	2 (1%)	5 (1%)	··
Duration of isoniazid use, months*	13·2 (±4·8)	11·4 (±6·1)	0·08
Concurrent vitamin B6 and isoniazid			
yes	104/161 (65%)	71/96 (74%)	0·003
Missing	7 (4%)	13 (14%)	··
Concurrent tuberculosis treatment and isoniazid†			
Yes	3/161 (2%)	6/96 (6%)	0·08
Missing	1 (1%)	0	··
HIV-positive			
Yes	171 (87%)	170 (22%)	<0·0001
Missing	1 (1%)	36 (4%)	··
Duration of HIV, years*	4·8 (±4·3)	5·8 (±5·7)	0·24
Antiretroviral therapy			
Yes	0/172	6/165 (3%)	0·01
Missing	2 (1%)	41 (20%)	··
Food security			
Secure	7 (4%)	112 (14%)	<0·0001
Mildly insecure	11 (6%)	86 (11%)	··
Moderately insecure	36 (18%)	211 (27%)	··
Severely insecure	141 (72%)	364 (47%)	··
Missing	2	8	··
Dietary diversity score			
≥median score (30·5)	64 (33%)	343 (44%)	0·004
<median score	133 (68%)	438 (56%)	··

	Patients with pellagra (n=197)	Healthy controls (n=781)	p value
Underweight[‡]			
Yes	27 (14%)	35 (5%)	<0·0001
Missing	1 (1%)	6 (1%)	··
Alcohol consumption in past 14 days			
None	185 (94%)	728 (93%)	0·10
Non-excessive	6 (3%)	43 (6%)	··
Excessive	6 (3%)	10 (1%)	··
Referral status			
Walk-in patient	79 (40%)	673 (86%)	<0·0001
Referral	118 (60%)	108 (14%)	··
Additional medications[§]			
≥1 medication	14 (7%)	51 (7%)	0·75
Missing	0	1 (0%)	··
Maize source[¶]			
Probably fortified	7 (4%)	32 (4%)	0·84
Probably not fortified	190 (97%)	745 (95%)	··
Missing	0	4 (1%)	··
Household food aid in past year			
Yes	13 (7%)	35(4%)	0·27
Missing	0	4(1%)	··
Regular income[‖]			
Yes	126/196 (64%)	580/777 (75%)	0·005
Symptoms in past 7 days			
Glossitis or oral lesions	91 (46%)	44 (6%)	<0·0001
Diarrhoea[**]	59 (30%)	··	··
Weakness	104 (53%)	116 (15%)	<0·0001
Missing	0	3 (0%)	··
Depressed mood	87 (44%)	146 (19%)	<0·0001
Anorexia	90 (46%)	170 (22%)	<0·0001
Missing	1 (1%)	0	··
Confusion or altered mental status[**]	77 (39%)	··	··
Missing	1 (1%)	··	··
Insomnia	70 (36%)	179 (23%)	0·0005
Anxiety or agitation	70 (36%)	153 (20%)	<0·0001
Nausea, dyspepsia, or emesis	98 (50%)	189 (24%)	<0·0001
Dizziness	82 (42%)	152 (20%)	<0·0001
Missing	2 (1%)	0	··
Arthralgia	87 (44%)	224 (29%)	<0·0001
Missing	0	3 (0%)	··
Headache	101 (51%)	408 (52%)	0·81
Peripheral neuritis	100 (51%)	169 (22%)	<0·0001

Data are n/N (%) or mean (SD), unless otherwise stated. The Fisher exact test compared proportions and the *t* test compared means between people with pellagra and healthy controls at study enrolment.

[*] Integer-valued covariate treated as continuous; odds ratio indicates the change in odds per each unit increase in the covariate.

[†] Concurrent tuberculosis disease treatment included multiple drugs, of which one was isoniazid.

[‡] Underweight was defined as a body-mass index <18·5 kg/m^2 or, for pregnant women, mid-upper-arm circumference<23 cm.

[§] Not including medications used for treating tuberculosis or HIV disease.

[¶] Home or locally milled maize were considered unlikely to be fortified.

[‖] Among enrolees older than 15 years.

[**] Diarrhoea and altered mental status were exclusionary criteria for control enrolment and are therefore not reported here.

Table 2:

Unadjusted and adjusted odds of having pellagra by isoniazid exposure status and covariates for all enrolees

	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Isoniazid use in past 2 months		
No	1 (ref)	1 (ref)
Yes	42·4 (22·9–78·5)	42·6 (13·3–136·6)
HIV-positive *		
No	1 (ref)	1 (ref)
Yes	31·0 (17·1–56·0)	3·2 (1·0–9·7)
Food security		
Secure	1 (ref)	1 (ref)
Mildly insecure	2·1 (0·8–5·9)	5·6 (1·0–32·1)
Moderately insecure	3·0 (1·3–7·1)	6·2 (1·4–28·5)
Severely insecure	7·3 (3·2–16·5)	6·6 (1·5–28·8)
Dietary diversity score		
≥median score (30·5)	1 (ref)	1 (ref)
<median score	1·6 (1·2–2·3)	1·8 (0·9–3·3)
Underweight †		
No	1 (ref)	1 (ref)
Yes	3·3 (1·9–5·8)	4·0 (1·6–10·0)
Alcohol consumption in past 14 days		
None	1 (ref)	1 (ref)
Non-excessive	0·5 (0·2–1·3)	1·2 (0·3–4·5)
Excessive	2·6 (0·9–7·7)	27·4 (4·6–162·6)
Referral status		
Walk-in patient	1 (ref)	1 (ref)
Referral	9·4 (6·4–13·7)	11·4 (5·5–23·4)
Additional medications ‡		
None	1 (ref)	1 (ref)
≥1 medication	1·1 (0·6–2·0)	1·3 (0·4–4·1)
Maize source		
Probably fortified	1 (ref)	1 (ref)
Probably not fortified§	1·2 (0·5–2·7)	0·4 (0·1–2·4)
Household food aid in past year		
No	1 (ref)	1 (ref)
Yes	1·5 (0·8–3·0)	1·0 (0·3–3·9)
Regular income ¶		
No	1 (ref)	1 (ref)
Yes	0·5 (0·4–0·8)	0·6 (0·3–1·3)

All missing values underwent multiple imputation before the analysis.

[*] HIV was collinear with isoniazid exposure within 2 months (Phi=0·54).

[†] Underweight was defined as a body-mass index <18·5 kg/m^2 or, for pregnant women, mid-upper-arm circumference <23 cm.

[‡] Not including medications used for treating tuberculosis or HIV disease.

[§] Home or locally milled maize were considered unlikely to be fortified.

[¶] Among enrolees older than 15 years.