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Outcomes of isoniazid prophylaxis among HIV-infected children attending routine HIV care in Kenya

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Setting: Three human immunodeficiency virus (HIV) care clinics in Eastern Province, Kenya.

Objectives: To establish rates of treatment completion, loss to follow-up, adverse drug reactions, tuberculosis (TB) disease and mortality among 606 HIV-infected children during 6 months of isoniazid preventive therapy (IPT).

Design: Retrospective record review.

Results: Of 606 HIV-infected children started on IPT, 556 (91.7%) successfully completed treatment, while 20 (3.3%) completed with interruptions. Cumulatively, 30 children (4.9%) did not complete IPT: 4 (0.7%) were lost to follow-up, 4 (0.7%) discontinued because of treatment interruptions, 2 (0.3%) developed adverse drug reactions, 1 developed a chronic cough, 1 was transferred to a non-IPT facility and 18 (3%) developed TB, including 2 who eventually died. TB disease was diagnosed in a median of 3 weeks (interquartile range [IQR] 2–16) post-IPT initiation. The median CD4 cell count for those aged 1–4 years who developed TB disease was 1023 cells/mm^3 (IQR 375–1432), while for those aged 5–14 years it was 149 cells/mm^3 (IQR 16–332). Isoniazid resistance was not detected in the four culture-confirmed TB cases.

Conclusion: The high treatment completion, low loss to follow-up rate and few adverse drug reactions affirm the feasibility of IPT provision to children in HIV care clinics.

Human immunodeficiency virus (HIV) infection remains the strongest risk factor for developing tuberculosis (TB) disease in those with latent or new tuberculous infection.[1] There is an estimated 20-fold increase in TB incidence among HIV-infected children compared to non-HIV-infected children.[2] Although the World Health Organization recommends the administration of isoniazid preventive therapy (IPT) to reduce the risk of TB, IPT uptake remains low.[3] In 2010, only 178 000 HIV-infected individuals received IPT worldwide.[4]

In Kenya, IPT provision in HIV care clinics lags behind set targets due to concerns related to the feasibility of its implementation. In 2011, the TB and HIV control programmes commenced IPT implementation in selected HIV care clinics in public hospitals in Kenya. The purpose was to gain local programmatic experience that would inform widespread IPT scale-up in routine clinical settings.

In the present study, we report outcomes from three HIV care clinics providing IPT to children in the Eastern Province, Kenya. First, we established the IPT completion rate and loss to follow-up rate among HIV-infected children during the 6 months of IPT. In addition, we determined the rate of development of adverse drug reactions (ADRs) among HIV-infected children. Lastly, we established the rate of development of TB disease, including its drug resistance pattern, and mortality among HIV-infected children during IPT.

METHODS

Study design, setting and population

We retrospectively reviewed patient records in three HIV care clinics of Kangundo, Makindu and Makueni District Hospitals in Eastern Province, Kenya. As of 1 September 2011, the three facilities had a cumulative total of 799 children enrolled in HIV care. The TB and HIV clinics in all the facilities are co-located, with co-infected patients receiving integrated care.[5] Multidisciplinary committees comprising service providers from both clinics and members of hospital management coordinate the provision of TB-HIV services.

Study participants were all HIV-infected children aged between 1 and 14 years started on IPT from 1 September 2011 and who had completed it by 30 November 2012.

Description of the IPT programme

Intensified case finding of TB in HIV patients commenced in May 2011, while the provision of IPT commenced in September 2011. Health care workers routinely screened all children enrolled in the HIV care clinic during monthly visits using a nationally developed standard TB symptom screening tool that inquired about presence of cough of any duration, history of household contact with a confirmed case of TB disease, fever (i.e., any reported hotness of the body or body temperature exceeding 37.5°C), and poor weight gain, defined as reported weight loss, or very low weight (weight-for-age less than −3 *Z*-score), or underweight (weight-for-age less than −2 *Z*-score), or confirmed weight loss (>5%) since the last visit, or growth curve flattening. A child without any of these symptoms/signs was offered IPT.

HIV-infected children aged <1 year (in accordance with the Kenya TB-HIV guidelines), TB suspects, those with TB disease, with active hepatitis, with symptoms of peripheral neuropathy and those who had been treated for TB in the past 2 years were excluded from IPT. Children with a previous history of poor adherence to highly active antiretroviral therapy (HAART) were also excluded, as they were deemed likely to have poor adherence to IPT.

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KEY WORDS
tuberculosis; isoniazid prophylaxis; treatment completion; loss to follow-up; adverse drug reactions

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Health education on the benefits of IPT was provided to the parents of all children enrolled in HIV care clinics. Consent was then sought and, with assistance of peer counsellors, health care workers conducted adherence counselling. Patient baseline details (name, age, sex, weight, type of HAART, most recent CD4 cell count) were recorded in the IPT register. A full patient pack of isoniazid (INH) containing 6 months of prophylaxis was constituted at the dose of 10 mg/kg/day. The INH patient packs were stored at the pharmacy, from where it was dispensed with other medication during scheduled HIV clinic days.

Monthly follow-up for INH pill refill, screening for TB, evaluation for ADRs and reinforcement of adherence counselling were conducted at the HIV care clinic as part of routine care. Evaluation for ADRs included assessment for hepatotoxity, peripheral neuropathy and skin rash. Routine biochemical monitoring for hepatotoxicity was not performed. If patients failed to attend scheduled clinics, attempts were made to bring them back to care using peer counsellors, and in line with the existing loss to follow-up prevention mechanisms.

Measurements of outcomes and definitions

Successful completion of IPT was defined as taking all doses within 6 months. The duration of IPT was extended beyond 6 months for those who interrupted treatment by assigning an equivalent extra number of days. Loss to follow-up was defined as no clinic attendance for ⩾3 months. Any death occurring during the 6 months of treatment, regardless of cause, was recorded as mortality.

Data collection, entry and analysis

Data were collected between December 2012 and January 2013 using a structured form designed for the study. Study investigators retrieved information about study variables for each child using the facility IPT register. The variables collected for each child were age in years, sex, whether or not on HAART, CD4 cell count at start of prophylaxis and information related to the occurrence of outcomes (treatment interruptions, ADRs, deaths, TB disease, loss to follow-up).

We conducted data analysis using EpiData software (EpiData Association, Odense, Denmark). The abstracted data were double-entered, verified and analysed. We performed descriptive statistical analysis in relation to the study objectives. We examined the relationship between the development of TB disease while on IPT, as well as clinical variables of age (for this purpose categorised as ⩽5 and >5 years), sex and CD4 cell count on the other hand. The level of significance was set at 5%.

Ethics

The study was reviewed by the Ministry of Health and the Division of Leprosy, Tuberculosis and Lung Disease, Nairobi, Kenya, and approved as evaluation of a public health programme.

RESULTS

A total of 606 HIV-infected children were initiated on IPT in the three HIV care clinics. The median age was 8 years (interquartile range [IQR] 5–11). The largest age group was 5–9 years (n = 280), followed by 10–14 years (n = 222) and 1–4 years (n = 104). Demographic and baseline characteristics are shown in Table 1.

Of the 606 children, 556 (91.7%) successfully completed IPT by taking all of the doses within 6 months. A further 20 (3.3%) completed IPT after their duration was extended beyond 6 months to compensate for minor treatment interruptions. The cumulative treatment completion rate was therefore 95%. A total of 24 children (4%) had treatment interruptions of a median of 9 days (IQR 5–33); of these, 18 (75%) were from a single HIV care clinic.

TABLE 1 Baseline demographic and clinical characteristics of children (N = 606) on isoniazid preventive therapy

Characteristic	
Sex, %	
Female	58.8
Male	41.2
On HAART, *n* (%)	568 (93.7)
Age, years, median [IQR]	8 [5–11]
Initial CD4 count, cells/mm^3, mean (minimum–maximum)	
Children aged 1–5 years	1183 (153–2698)
Children aged 6–14 years	763 (2–2856)

HAART = highly active antiretroviral therapy; IQR = interquartile range.

Cumulatively, 30 children (4.9%) did not complete IPT (Figure). Four (0.7%) discontinued due to treatment interruptions, and 4 (0.7%) were lost to follow-up. ADRs were reported in two children (0.3%), both female, aged 7 and 11 years, on zidovudine (ZDV), lamivudine (3TC) and nevirapine (NVP), with CD4 cell counts of respectively 568 and 691 cells/mm^3 at the start of IPT. The first child developed jaundice, nausea and ascites during the fourth week of INH prophylaxis. The second developed jaundice on the second week of prophylaxis. Symptoms resolved after stopping all the medications in both instances. Liver function tests were not conducted (Table 2).

During the 6 months of IPT, 18 children (3%) developed TB disease. Their mean baseline age was 8.3 years (range 3–14); 67% were female. Four TB cases were bacteriologically confirmed using sputum culture, and 14 were defined as probable (i.e., they fulfilled the Kenya national diagnostic criteria for children). Fifteen of the children (83.3%) who developed TB were on HAART. The median CD4 cell count for those aged 1–4 years who developed TB disease was 1023 cells/mm^3 (IQR 375–1432), while the median CD4 cell count for those aged 5–14 years who developed TB disease was 149 cells/mm^3 (IQR 16–332). The overall median time to diagnosis of TB disease in all the 18 cases was 3 weeks (IQR 2–7) from IPT initiation, with 13 cases (72%) diagnosed within 5 weeks of IPT initiation. INH resistance was undetected among the *Mycobacterium tuberculosis* isolates of the four cases of TB disease confirmed using culture. Sixteen children diagnosed with TB during IPT successfully completed anti-tuberculosis treatment, while two died. The odds of being diagnosed with TB disease while on IPT for children aged >5 years was 4.19 times higher compared to children aged ⩽5 years (odds ratio [OR] 4.19, 95% confidence interval [CI] 1.07–16.38). In children with CD4 cell count > 500 cells/ml^3, for every unit increase in CD cell count there was a 7% decrease in the odds of developing TB while on IPT compared to a 3% decrease in those with CD4 cell counts of <500 cells/ml^3 (OR 0.87, 95%CI 0.39–0.96 vs. OR 0.996, 95%CI 0.995–0.999). Although the difference was not statistically significant, males were 31% less likely to develop TB compared to females (OR 0.68, 95%CI 0.26–2.28).

There were two deaths (0.3%), occurring during the seventh and twelfth weeks of IPT, 1 female and 1 male, aged respectively 6 and 9 years. Both were on antiretroviral drugs ZDV, 3TC and NVP, with CD4 cell counts of respectively 149 and 201 cells/mm^3 at the start of IPT. Although they had previously been diagnosed with TB disease, the definite cause of both deaths was not ascertained.

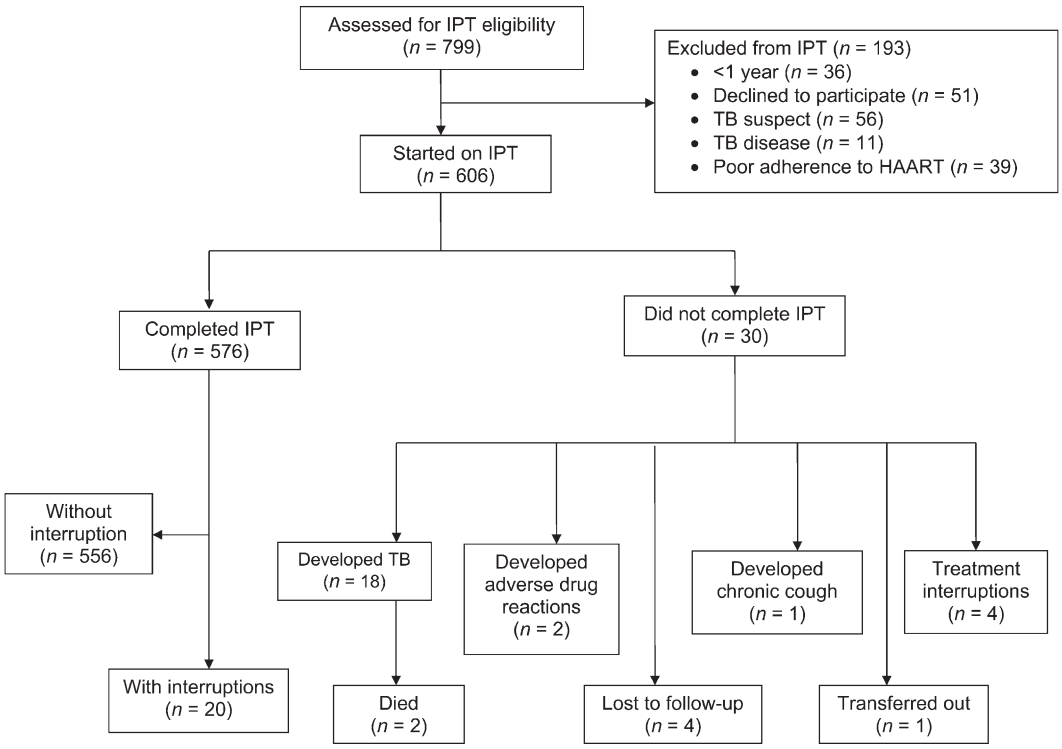

FIGURE Flow chart showing IPT implementation and outcomes. IPT = isoniazid preventive therapy; TB = tuberculosis; HAART = highly active antiretroviral therapy.

TABLE 2 Reasons for discontinuation of IPT among the HIV-infected children

Reason for discontinuation	Children *n* (%)
Developed tuberculosis	18 (60.0)
Developed chronic cough	1 (3.3)
Adverse drug reactions	2 (6.7)
Frequent treatment interruptions	4 (13.3)
Transferred to non-IPT site	1 (3.3)
Lost to follow-up	4 (13.3)
Total	30

IPT = isoniazid preventive therapy; HIV = human immunodeficiency virus.

DISCUSSION

This study, representing a large cohort of HIV-infected children, is the first to describe IPT outcomes in routine HIV care in Kenya. It documents a 91.7% IPT completion rate and 0.7% loss to follow-up rate, while ADRs and deaths were reported in 0.3%. In addition, 3% of the children were diagnosed with TB disease during IPT.

The impressive IPT completion rate in this study was possibly due to its integration in HIV clinics with a pre-existing patient retention mechanism.[6] However, patient retention strategies are not standardised in Kenya;[7] there may therefore be risks to IPT completion in HIV care clinics with poor performance. Unsurprisingly, 75% of children who had treatment interruptions in the present study were from a single HIV care clinic that has a documented high percentage of loss to follow-up among general HIV care clinic attendees.[5] Although we were unable to determine adherence, the fact that IPT was dispensed as part of antiretroviral therapy gives us reason to believe the drugs may actually have been taken by the patients and provides a strong case for IPT provision as part of routine HIV care. The study also shows that through selection of children with a previous history of good adherence to HAART, a high IPT completion rate is achievable.

ADRs were reported in two children (0.3%) who were on concomitant hepatotoxic medications, probably confirming the findings of other studies on the safety of IPT.[8,9] However, pharmacovigilance in this setting was anchored on health provider inquiry of symptoms and patient/guardian self-reporting of symptoms, which may have resulted in a low reporting rate. Nevertheless, these findings are comparable to results in Guinea Bissau, where excellent safety of IPT was reported in a study of HIV-positive children, suggesting that in general INH prophylaxis is safe in children.[10] A study from South Africa also reported no side effects among 180 children enrolled in INH treatment,[11] with another study reporting 0% liver injury in children aged 0–14 years.[12]

In this study, TB disease was predominantly diagnosed in children with severe immunosuppression. The median time to diagnosis from IPT initiation was 3 weeks, with the overwhelming majority (72%) of these cases diagnosed within 5 weeks of IPT initiation. This shows the likely pre-existence of the disease prior to IPT initiation and suggests that although symptom screening may work well in children with higher CD4 cell counts, its utility may be limited in those with severe immunosuppression. These findings are not particularly surprising, considering a report from Rwanda on TB screening among HIV-infected children using a symptom screen that found that although 95% of children likely to have TB were successfully identified, 5% of the children likely to have the disease were missed.[1] A South African study suggested that signs and symptoms were poor predictors of TB among HIV-infected children and failed to identify a large proportion of HIV-infected children with TB when used as a screening tool.[13] In the light of these findings, Kenyan policy should consider the

addition of chest radiography to screening requirements, especially among severely immunosuppressed children. However, such policy direction may have implications on further roll-out of IPT to peripheral health facilities without radiographic equipment.

In the present study, INH resistance was not detected among the *M. tuberculosis* isolates for the four cases of culture-confirmed TB disease. We hypothesise that as a large majority of children who developed TB (72%) were diagnosed within 5 weeks of IPT initiation, it limited the potential duration of INH monotherapy for undiagnosed disease, thereby reducing the risk of developing drug resistance. This affirms the critical importance of routine TB screening during IPT.

It is difficult to draw inferences about mortality in children given IPT from this study, as the causes of the two deaths remained uncertain. There is also a paucity of comparable mortality data on children enrolled on IPT. However, these events, although not directly attributable to IPT, represent a rate of 330 per 100 000 children initiated on IPT, comparable to that in Botswana of 50/100 000 in an adult population.[14]

Our study findings are subject to some limitations. First, this was a retrospective record review, with a limited number of variables available for abstraction. We could therefore not determine adherence to IPT. Second, the availability of absolute CD4 cell count only for children aged <5 years may have affected the analysis and inferences made about the development of TB in this group.

The study has implications on the TB-HIV programme in Kenya. First, our findings of a high treatment completion rate, low loss to follow-up and good safety should provide motivation for programme managers in similar low-income settings to scale up IPT as part of routine HIV care. However, because HIV care clinics with poor general client retention may have lower IPT completion rates, caution is advised in implementation. Second, incident TB during the first weeks of IPT provision suggests that the symptom screening tool may be in need of revision to enhance its utility in severely immunocompromised children. In conclusion, we find that IPT provision to HIV-infected children in routine HIV care clinics is feasible.

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Contexte : Trois dispensaires de soins pour le virus de l'immunodéficience humaine (VIH) dans la Province Est du Kenya.
Objectifs : Mettre en évidence des taux d'achèvement du traitement, de perte du suivi, de réactions indésirables, de maladie tuberculeuse et de mortalité chez 606 enfants infectés par le VIH au cours de 6 mois de traitement préventif à l'isoniazide (IPT).
Schéma : Revue rétrospective des dossiers.
Résultats : Sur 606 enfants infectés par le VIH et mis sous IPT, 556 ont réussi à compléter leur traitement (91,7%), alors que 20 (3,3%) l'ont achevé mais avec des interruptions. Au total, 30 enfants (4,9%) n'ont pas achevé le traitement : parmi ceux-ci, 4 (0,7%) ont été perdus lors du suivi, 4 (0,7%) ont interrompu le traitement, 2 (0,3%) ont rencontré des effets indésirables des médicaments, 1 une toux chronique, 1 a été transféré vers un service non-IPT et chez 18 (3%) on a vu apparaître une tuberculose (TB), incluant 2 qui sont décédés. La maladie TB a été diagnostiquée après une durée médiane de 3 semaines (limites interquartiles [IQR] 2 à 16) après l'initiation de l'IPT. Le décompte médian de cellules CD4 pour les enfants âgés de 1 à 4 ans, chez qui la TB est apparue, était de 1023 cellules/mm^3 (IQR 375–1432) alors que chez ceux âgés de 5 à 14 ans, il y avait 149 cellules/mm^3 (IQR 16–332). On n'a pas détecté de résistance à l'isoniazide dans les quatre cas de TB confirmés par la culture.
Conclusion : Le taux élevé d'achèvement du traitement et le faible taux de pertes de suivi et de réactions indésirables aux médicaments confirment la faisabilité de l'administration de l'IPT aux enfants dans les dispensaires de soins VIH.

Marco de referencia: Tres consultorios de atención de la infección por el virus de la inmunodeficiencia humana (VIH) en la Provincia Oriental de Kenia.
Objetivos: Establecer en un grupo de 606 niños infectados por el VIH las tasas de compleción del tratamiento antituberculoso, pérdida durante el seguimiento, reacciones adversas a los medicamentos, enfermedad tuberculosa y de mortalidad durante los 6 meses del tratamiento preventivo con isoniazida (IPT).
Método: Fue este un examen retrospectivo de las historias clínicas.
Resultados: De los 606 niños con infección por el VIH que comenzaron el IPT, 556 lo completaron con éxito (91,7%) y 20 lo completaron con interrupciones (3,3%). Según el análisis acumulado, 30 niños no completaron el tratamiento (4,9%); 4 se perdieron de vista durante el tratamiento (0,7%), 4 se excluyeron por interrupciones del tratamiento (0,7%), 2 presentaron reacciones adversas a los medicamentos (0,3%), 1 presentó tos crónica, 1 se trasladó a un

centro que no suministraba el IPT, 18 contrajeron la enfermedad tuberculosa (3%) y de ellos 2 fallecieron. La mediana del lapso hasta el diagnóstico de la tuberculosis (TB) fue 3 semanas (intervalo intercuartil [IQR] 2–16) después de haber iniciado el IPT. La mediana del recuento de células CD4 en los niños que contrajeron la enfermedad del subgrupo entre 1 y 4 años de edad fue 1023 células/mm^3 (IQR 375–1432) y en el subgrupo de 5 a 14 años fue 149 células/mm^3 (IQR 16–332). No se detectó resistencia a isoniazida en ninguno de los cuatro casos de TB confirmados por cultivo.

Conclusión: El alta tasa de compleción del tratamiento, la baja proporción de pérdidas de vista durante el seguimiento y las escasas reacciones adversas que se observaron confirman la viabilidad de la provisión del IPT a los niños en los consultorios de atención de la infección por el VIH.

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