INT J TUBERC LUNG DIS 14(2):197–202

Outcomes and safety of concomitant nevirapine and rifampicin treatment under programme conditions in Malawi

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SUMMARY

SETTING: Thyolo District Hospital, rural Malawi.

OBJECTIVES: To report on 1) clinical, immunological and virological outcomes and 2) safety among human immunodeficiency virus (HIV) infected patients with tuberculosis (TB) who received concurrent nevirapine (NVP) and rifampicin (RMP) based treatment.

DESIGN: Retrospective cohort study.

METHODS: Analysis of programme data, June–December 2007.

RESULTS: Of a total of 156 HIV-infected TB patients who started NVP-based antiretroviral treatment, 136 (87%) completed TB treatment successfully, 16 (10%) died and 5 (4%) were transferred out. Mean body weight and CD4 gain (adults) were respectively 4.4 kg (95%CI 3.3–5.4) and 140 cells/mm^3 (95%CI 117–162). Seventy-four per cent of patients who completed TB treatment and had a viral load performed (n = 74) had undetectable levels (<50 copies/ml), while 17 (22%) had a viral load of 50–1000 copies/ml. Hepatotoxicity was present in 2 (1.3%) patients at baseline. Two patients developed Grade 2 and one developed Grade 3 alanine transaminase enzyme elevations during TB treatment (incidence rate per 10 years of follow-up 4.2, 95%CI 1.4–13.1). There were no reported deaths linked to hepatotoxicity.

CONCLUSIONS: In a rural district in Malawi, concomitant NVP and RMP treatment is associated with good TB treatment outcomes and appears safe. Further follow-up of patients would be useful to ascertain the longer-term effects of this concurrent treatment.

KEY WORDS: Malawi; HIV; tuberculosis; nevirapine; rifampicin; alanine transferase

IN MALAWI, a small resource-limited country in sub-Saharan Africa, 77% of newly registered tuberculosis (TB) patients are also infected by human immunodeficiency virus type 1 (HIV-1).[1] Mortality during the course of anti-tuberculosis treatment in such patients (case fatality) is high, and attributed to HIV-related opportunistic infections.[2] It is believed that antiretroviral treatment (ART) offered to HIV-positive TB patients reduces mortality and improves overall survival.

Malawi currently uses a fixed-dose combination of stavudine (d4T), lamivudine (3TC) and nevirapine (NVP) as its first-line ART regimen,[3] and rifampicin (RMP) based drugs for the treatment of TB.[4] RMP is a potent inducer of the liver enzyme cytochrome CYP 450, responsible for the metabolism of non-nucleoside reverse transcriptase inhibitors (NNRTI) such as NVP and efavirenz (EFV). Plasma concentrations of NVP and EFV may thus be reduced when used concomitantly with RMP, and this in turn may lead to sub-optimal drug (NVP or EFV) exposure, treatment failure and emerging drug resistance.[5] Increasing the dose of NVP or EFV to compensate for this interaction increases the potential risk of toxicity and is thus not advised in recent World Health Organization (WHO) guidelines.[6]

Although EFV is considered the first choice for use in ART regimens along with RMP-based TB treatment, the Ministry of Health of Malawi opted to use its standardised first-line ART regimen (containing NVP) also for co-infected TB patients, and this is what is recommended as the national protocol.[3] This decision was made on the basis that 1) EFV is teratogenic, and nationally more than half of all HIV-infected TB patients are women of child-bearing age; with evident gaps in access to effective contraception at health centre level in Malawi, there is a real risk that mothers can become pregnant during anti-tuberculosis treatment and ART; 2) EFV is not available in a generic fixed-drug combination tablet and higher pill

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Article submitted 23 July 2009. Final version accepted 11 September 2009.

counts are involved, which may influence adherence and complicate drug logistics; 3) EFV is considerably more expensive; 4) EFV cannot be used in children aged <3 years; and 5) a number of studies have shown that although plasma NVP levels are reduced by RMP, they still remain within the effective range and there is thus no significant effect on the clinical or virological impact of the drug.[7–12]

Expert opinion is still divided on the clinical and virological efficacy of NVP with RMP in TB patients. There is also concern that the use of NVP under programme conditions might be associated with a relatively higher risk of hepatotoxicity.

Published information on these issues from programme settings in sub-Saharan Africa is limited. Among HIV-infected patients with TB who received concurrent NVP- and RMP-based treatment under routine programme conditions, we thus report on 1) clinical, immunological and virological outcomes and 2) safety—the incidence of hepatotoxicity and other reported side effects.

METHODS

Design

Retrospective cohort study using routine programme data.

Study setting and population

This study was conducted in Thyolo District, one of the largest rural districts in southern Malawi with about 587 000 inhabitants.[13] The district has one main public hospital and 29 health centres. This study included all ART-naïve adult HIV-infected new TB patients registered at Thyolo District hospital between June and December 2007 who received TB treatment along with NVP-based ART.

Management of the TB-HIV co-infected patient

TB patients are diagnosed, registered and treated according to national[3,4] and WHO[14] guidelines. TB treatment for new patients includes a 2-month initial phase of RMP, isoniazid (INH) and pyrazinamide (PZA), with additional ethambutol for sputum smear-positive patients, followed by a 4-month continuation phase of INH and RMP.

Newly diagnosed TB patients receive HIV testing and counselling. Those who are HIV-positive are offered cotrimoxazole prophylaxis if there are no contraindications. The timing of ART initiation is based on the degree of immune-deficiency: patients with CD4 count < 200 cells/mm^3 start ART as soon as they are stabilised on TB treatment (usually between 2 and 8 weeks); patients with a CD4 count of 200–350 cells/mm^3 start ART on completion of the intensive phase of anti-tuberculosis treatment (usually after 8 weeks); and those with CD4 counts > 350 cells/mm^3 start ART after completion of anti-tuberculosis treatment. First-line ART in Malawi consists of a fixed-dose combination of d4T+3TC+NVP, using zidovudine (AZT) and efavirenz (EFV) as alternatives in cases of d4T and NVP-related side-effects.[3] Once started on ART, patients are reviewed 2 weeks later and then once monthly, provided there are no complications or drug side-effects. Pyridoxine prophylaxis is systematically offered to reduce the incidence of peripheral neuropathy. TB treatment and ART are offered free of charge in Thyolo.

Clinical, immunological and virological outcomes

TB treatment outcomes were defined as cured if a sputum smear-positive patient became smear-negative on completion of TB treatment; completed treatment if a patient completed the full course of TB treatment without sputum confirmation; dead if a patient died for any reason while on treatment; lost to follow-up if a patient did not attend the clinic for ⩾2 months after the scheduled follow-up appointment; stopped treatment if a patient was known to have stopped treatment for any reason during treatment; or transferred out if a patient had transferred out permanently to another treatment facility. As Thyolo has a well developed network of community volunteers and nurses who follow patients up at home, reliable ascertainment of deaths is possible.[15]

Weight and CD4 count (measured using the Partec Cyflow Counter, Partec GmbH, Münster, Germany) were measured at baseline and at the end of TB treatment. Viral load (measured using the Roche Amplicor polymerase chain reaction technique [Roche, Grenzach-Whylen, Germany]) was measured at the end of TB treatment (viral load <50 copies/ml = undetectable threshold), with all patients completing treatment requested to return to Thyolo hospital for this. The theoretical cut-off time for determining virological failure was set to be the end of anti-tuberculosis treatment, and thus 6 months or 24 weeks from the date of starting anti-tuberculosis treatment.

Hepatotoxicity and other side effects

Alanine transferase (ALT) levels were measured at baseline, at 1, 2 and 3 months and at the end of TB treatment to measure hepatotoxicity events, which were classified by grade according to the AIDS Clinical Trials Group (ACTG)[3] as follows: Grade 0 (<1.25 × upper limit of normal [ULN < 40 U/ml]), Grade 1 (1.25–2.5 × ULN), Grade 2 (2.6–5 × ULN), Grade 3 (5.1–10 × ULN), Grade 4 (>10 × ULN). Hepatotoxicity was defined as ALT elevations ⩾ Grade 2. Patients were monitored clinically for other side effects and these were reported in the patient file. Peripheral neuropathy was diagnosed if the patient complained of pain, paraesthesiae, numbness or weakness of the lower limbs.[3]

Data collection and statistical analysis

Structured forms were used to gather patient information. Data were entered into standardised monitoring

software (Fuchia, Epicentre, Paris, France). A χ^2 test was used to examine differences between proportions; the level of significance was set at $P \leqslant 0.05$ and 95% confidence intervals (CIs) were used throughout. Data were analysed using STATA/IC 10.0 software (Stata Corporation, College Station, TX, USA).

Ethical approval

General measures are provided in the Thyolo District ART facilities to ensure patient confidentiality, consent for HIV testing, and counselling and support for those who receive a positive HIV test result. The data in this study did not include patient identifiers. The Malawi National Health Science Research Committee provides general oversight and approval for the collection and use of routine programmatic data for monitoring and evaluation, and does not require a formal submission for ethical approval for the type of study conducted in this paper, as the procedures were in line with the recommended national protocol.[3] This study was nevertheless submitted to and received ethical approval from the independent ethical review board of Médecins sans Frontières, Belgium, and the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris.

RESULTS

Characteristics of the study population

A total of 170 HIV-infected TB patients started ART after being diagnosed with TB during the study period. Of these, 14 had missing data for TB outcome or date of outcome and were excluded from the analysis. Table 1 shows the baseline socio-demographic characteristics as well as nutritional status, TB type, baseline CD4 and ALT levels of the 156 patients included in the study. Malnutrition was assessed using body mass index (BMI), defined as weight in kg divided by height in m². An adult with a BMI of <18.5 kg/m² was considered to be malnourished; this was the case in 48% of adult TB patients. All patients were started on an ART regimen of d4T+3TC+NVP. Patients with CD4 count < 200 cells/mm³ initiated ART after a median of 14 (interquartile range [IQR] 13–15) days from the time of starting TB treatment and patients with CD4 ⩾ 200–350 cells/mm³ after a median of 55 days (IQR 54–56), in accordance with clinical guidelines. Patients were on concurrent TB treatment and ART for a median of 5 months (IQR 3.8–5.5).

Clinical, immunological and virological outcomes

Table 2 shows standardised TB outcomes for patients on concurrent TB treatment and ART. The treatment success rate was 87%, while 10% of patients died during the course of anti-tuberculosis treatment. Patient deaths occurred a median of 1.7 months (IQR 0.5–3.1) after starting TB treatment. A higher proportion of older patients (⩾40 years) died than younger patients (<40 years), (17% vs. 7%, $P = 0.05$), and a higher proportion of patients with CD4 < 200 cells/mm³ died than those with CD4 ⩾ 200 cells/mm³ (100% vs. 0%, $P = 0.02$, data not shown).

Table 3 shows weight gain, immunological recovery and end of treatment viral loads for those patients who completed TB treatment successfully. The mean increase in body weight among adults was 4.4 kg (95%CI 3.3–5.5) and among children, 1.7 kg (95% CI 6.6–9.9). Mean increase in CD4 count from baseline

Table 1 Baseline socio-demographic characteristics, nutritional status, TB type, baseline CD4 and ALT levels of HIV-infected TB patients receiving concurrent TB treatment and ART, Thyolo, Malawi

Variable	*n* (%)
Total	156
Sex	
Females	71 (45.5)
Males	85 (54.5)
Age, years	
<15	6 (3.9)
15–29	34 (21.8)
30–39	63 (40.4)
⩾40	53 (34.0)
Median [IQR]	35 [29–42]
TB type	
Smear-positive PTB	66 (42.3)
Smear-negative PTB	65 (41.7)
EPTB	25 (16.0)
CD4 cell count, cells/mm³	
Adults ($n = 150$)	
<50	38 (25.3)
50–199	79 (52.7)
200–349	30 (20.0)
⩾350	3 (2.0)
Median [IQR]	113 [47–186]
Children ($n = 6$)*	
Median [IQR]	520 [212–732]
BMI, kg/m²†	
<16.0	20 (13.4)
16–18.49	53 (35.5)
⩾18.5	76 (51.0)
Median [IQR]	18.5 [16.7–20.4]
Baseline ALT levels‡	
Grade 0	148 (97.4)
Grade 1	2 (1.3)
Grade 2	1 (0.7)
Grade 3	0
Grade 4	1 (0.7)

*1 unknown record.
†7 unknown records.
‡4 unknown records.
TB = tuberculosis; ALT = alanine transferase; HIV = human immunodeficiency virus; ART = antiretroviral treatment; IQR = interquartile range; PTB = pulmonary TB; EPTB = extra-pulmonary TB; BMI = body mass index.

Table 2 TB treatment outcomes for patients on concurrent TB treatment and ART, Thyolo, Malawi ($N = 156$)

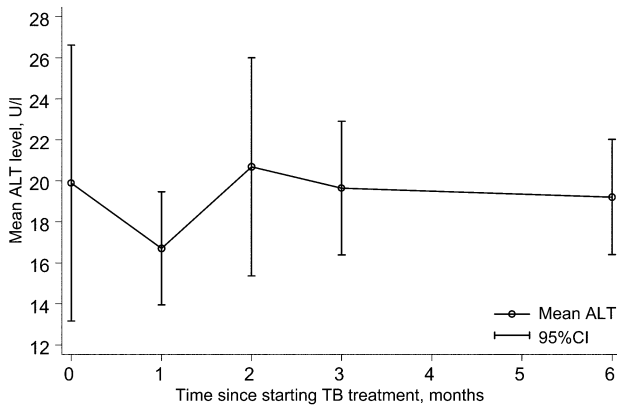
TB treatment outcome	*n* (%)
Treatment success*	136 (87.1)
Died	16 (10.3)
Lost to follow-up	0
Transferred out	4 (2.6)

*Includes patients who were cured (sputum confirmed negative) and patients who completed tuberculosis treatment.
TB = tuberculosis; ART = antiretroviral treatment.

Table 3 Weight gain, immunological recovery and viral loads at the end of TB treatment (n = 136)

Outcome	
Body weight, kg, mean increase (95%CI)	
Adults (n = 108/131)	4.4 (3.3–5.4)
Children (n = 2/6)	1.7 (−6.6–9.9)
CD4 count, cells/mm^3, mean increase (95%CI)	
Adults (n = 83/131)	140 (117–162)
Children (n = 0/6)	—
Viral load at the end of treatment, n (%)	
Adults (n = 76/131)	
Undetectable (<50 copies/ml)	56 (73.7)
50–999 copies/ml	17 (22.4)
1000–9999 copies/ml	1 (1.3)
⩾10 000 copies/ml	2 (2.6)
Children (n = 0/6)	—

TB = tuberculosis; CI = confidence interval.



Time, months	0 *n/N* (%)	1 *n/N* (%)	2 *n/N* (%)	3 *n/N* (%)	6 *n/N* (%)
Number at risk*	152/156 148 (97.4)	112/152	90/150	64/143	86/136
Grade 0	2 (1.3)	107 (95.5)	87 (96.7)	62 (96.9)	84 (97.7)
Grade 1	1 (0.7)	4 (3.6)	1 (1.1)	2 (3.1)	2 (2.3)
Grade 2	0	1 (0.9)	1 (1.1)	0	0
Grade 3	1 (0.7)	0	1 (1.1)	0	0
Grade 4	–	0	0	0	0

Figure Mean ALT levels over time for patients on concurrent rifampicin and nevirapine treatment, Thyolo, Malawi. *ALT unknown for four patients. ALT = alanine transferase; TB = tuberculosis; CI = confidence interval.

was 140 cells/mm^3 (95% CI 117–162 cells/mm^3). Of the 136 patients treated successfully, 76 (56%) had viral load measured at the end of treatment and of these, 56 (74%) had an undetectable viral load (<50 copies/ml); 17 had a viral load of 50–999 copies/ml and three patients had viral loads > 1000 copies/ml. These three patients had been on ART for only between 5.5 and 5.7 months.

Hepatotoxicity and other reported drug side effects

At baseline, two (1.3%) patients had significantly elevated ALT levels (Grade 2 and above). This included one patient with a Grade 2 ALT elevation and one with a Grade 3 elevation. ART was deferred in the latter for 6 weeks, when ALT levels had dropped to normal. The patient was started on NVP-based ART and did not have any further ALT elevations. Two (1.3%) patients developed Grade 2 and one (0.6%) Grade 3 ALT elevations at 1 and 2 months after starting TB treatment (incidence rate per 10 years of follow-up 4.2, 95%CI 1.4–13.1).

The Figure shows mean ALT levels among patients during the period of TB treatment. The incidence of other drug-related side effects was very low: 8 (5%) patients presented with Grade 1 peripheral neuropathy (PN), 2 (1.3%) with Grade 2 PN, and 1 (0.6%) with Grade 1 rash. All the reported side effects occurred among patients with baseline CD4 count < 200 cells/mm^3. There were no deaths in patients who reported side effects.

DISCUSSION

This study showed that among HIV-infected TB patients receiving RMP-based TB treatment and NVP-based ART concurrently, 87% completed TB treatment successfully, with good gains in body weight and CD4 count (immunological recovery). Concurrent treatment using NVP and RMP also appears safe under programme conditions, with a low incidence of significant ALT elevations and other reported drug side effects.

Of TB patients who had viral load measured at the end of TB treatment, 76% had undetectable levels of HIV-1 virus, and this finding compares well with patients on ART (without concurrent RMP) in both industrialised[16] and other resource-limited countries.[17] However, recent data from South Africa suggest that patients receiving concurrent RMP and NVP-based ART had a higher risk of virological failure in the first 18 months of treatment compared to patients receiving only NVP-based ART.[18] It would thus be necessary to be cautious and follow these patients and report on their virological outcomes over a longer period. Our conclusions on viral loads are also limited by the fact that a considerable proportion of patients (42%) on decentralised follow-up at distant health facilities did not return to the Thyolo Hospital for blood collection. This is attributable to issues of distance and transport costs, where public transport networks are relatively expensive and poorly developed.[2,19] Our viral load data thus need to be interpreted with caution: there might be data bias, as we do not really know what proportion of missing viral load data could be equated to failure. This practical shortcoming highlights the urgent need for access to an easy to use point-of-care viral load test for rural areas such as Thyolo.

Furthermore, if we assume that viral loads of less than 1000 copies/ml might be related to 'blips' —a transient viraemia that returns spontaneously to undetectable levels without apparent clinical consequences[20]—there were three (4%) patients with viral load titres ⩾1000 copies/ml who did not manifest any clinical or immunological signs. We do not

know the reasons for this, but it could be related to high baseline viral load titres, insufficient time on ART, poor adherence, primary resistance or poor clinical reporting. Although this may not seem high at a programme level, on a national scale in Malawi the implications could be considerable. For example, with about 25 000 newly registered TB cases each year in Malawi (77% HIV prevalence), about 18 865 (98%) co-infected patients would be eligible for combined NVP and RMP treatment, of whom 755 might have virological failure that could be missed without a viral load test. The poor correlation of clinical, pill count monitoring, immunological and other existing forms of adherence monitoring with inadequate viral suppression has been shown in a study conducted in Blantyre, Malawi.[21] These short-comings again highlight the urgent need for access to an easy to use point-of-care viral load test.

The incidence of side effects with concomitant NVP and RMP treatment, particularly hepatotoxicity, is of critical importance in resource-limited district settings where laboratory facilities are limited. The data from this study are thus reassuring in that both baseline and 'on treatment' incidence of ALT elevations were very low and did not complicate patient management or safety. The findings are also consistent with findings from Spain[22] and recent operational data from Botswana, which showed excellent virological, immunological responses and safety among HIV-infected TB patients who received concomitant NVP-based ART and RMP-based TB treatment.[12] We also had a relatively low incidence of peripheral neuropathy.

An encouraging finding of this analysis is the relatively low TB case fatality rate of 10%, which is considerably lower than previously reported from Malawi.[2,23] This might be linked to the fact that 75% of the cohort with CD4 counts < 200 cells/mm^3 were started on ART within a median of 2 weeks, and this early initiation of ART might be influencing survival.[21]

The strengths of this study were that 1) outcomes were reliably ascertained using registers that are robust and regularly checked by supervision teams, deaths were reliably ascertained, and there were no patients lost to follow-up, and the zero loss to follow-up reflects the good interaction between health services and the community, with information about deaths being reliably ascertained and good tracing of late attendees;[15] and 2) the data come from a programme setting and therefore probably reflect the operational reality on the ground.

The limitations of the study are that 1) patients were followed up only until the end of TB treatment and we are thus unable to report on longer term virological outcomes; and 2) data were missing in terms of laboratory parameters, and in particularly viral loads, due to the fact that many patients did not return to the hospital for blood collection for viral load at the end of TB treatment.

Under programme conditions in a rural district in Malawi, concomitant NVP and RMP treatment is associated with good TB treatment outcomes and appears safe. Further follow-up of patients who complete TB treatment successfully would be useful to ascertain the longer term effects of this concurrent treatment.

Acknowledgements

The authors are grateful to the Thyolo District Hospital management and the Ministry of Health of Malawi for their collaboration and encouragement in trying to implement HIV/AIDS related activities, including ART for TB patients. The Thyolo district HIV/AIDS programme is supported by Médecins sans Frontières. The authors are also very grateful to EuropeAid, la Direction Générale de la Coopération au Développement (Belgium Government), the Childrens Investment Fund Foundation, ELMA Foundation, the Global Fund, the International Union Against Tuberculosis and Lung Disease, Paris, and the World Health Organization, for their continuing support for HIV/AIDS activities in Malawi.

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RÉSUMÉ

CONTEXTE : Hôpital de district de Thyolo, Malawi rural.
OBJECTIFS : Décrire 1) les ressources cliniques, immunologiques et virologiques ; et 2) le degré de sécurité chez les patients infectés par le virus de l'immunodéficience humaine (VIH) et atteints de tuberculose (TB) ayant subi un traitement basé simultanément sur la névirapine (NVP) et la rifampicine (RMP).
SCHÉMA : Etude rétrospective de cohorte.
MÉTHODES : Analyse des données du programme de juin à décembre 2007.
RÉSULTATS : Sur un total de 156 tuberculeux infectés par le VIH ayant débuté un traitement antirétroviral basé sur la NVP, 136 (87%) ont achevé leur traitement antituberculeux avec succès, 16 (10%) sont décédés et 5 (4%) ont été transférés ailleurs. L'augmentation moyenne du poids corporel a été de 4,4 kg (IC95% 3,3–5,4) et celle des CD4 de 140 cellules/mm³ (IC95% 117–162). Parmi les patients ayant achevé leur traitement TB et chez qui on a mesuré la charge virale, les niveaux de celle-ci étaient indétectables (<50 copies/ml) chez 74 (74%), alors qu'elle était de 50–1000 copies/ml chez 17 (22%). Une hépatotoxicité était présente chez deux (1,3%) patients au début. Des augmentations de l'enzyme alanine transaminase sont survenues au cours du traitement TB chez deux patients de degré 2 et chez un patient de degré 3 (taux d'incidence pour 10 ans de suivi = 4,2 ; IC95% 1,4–13,1). Aucun décès n'a été signalé par hépatotoxicité.
CONCLUSIONS : Dans un district rural du Malawi, le traitement concomitant par NVP et RMP va de pair avec de bons résultats du traitement TB et semble dépourvu de risque. Il serait utile de suivre plus longtemps les patients pour s'assurer des effets à plus long terme de ce traitement simultané.

RESUMEN

MARCO DE REFERENCIA: El hospital distrital de Thyolo en una zona rural de Malawi.
OBJETIVOS: Comunicar el desenlace desde el punto de vista clínico, inmunológico y virológico y la seguridad toxicológica del tratamiento, en pacientes con tuberculosis (TB), coinfectados por el virus de la inmunodeficiencia humana (VIH), que recibieron simultáneamente tratamientos a base de nevapirina (NVP) y rifampicina (RMP).
DISEÑO: Fue este un estudio retrospectivo de cohortes.
MÉTODOS: Se analizaron los datos del programa entre junio y diciembre del 2007.
RESULTADOS: De los 156 pacientes infectados por el VIH y con TB que comenzaron tratamiento antirretrovírico basado en NVP, 136 (87%) completaron con éxito el tratamiento antituberculoso, 16 (10%) fallecieron y 5 (4%) se transfirieron a otros centros. La media del aumento de peso corporal en los adultos fue 4,4 kg (IC95% 3,3–5,4) y del recuento de CD4 fue 140 células/mm³ (IC95% 117–162). Se midió la viremia en 76 pacientes que completaron el tratamiento antituberculoso: en 74% la viremia no alcanzó el umbral de detección (menos de 50 copias/ml) y en 17 (22%) se encontraron entre 50 y 1000 copias/ml. Antes de comenzar la pauta antituberculosa se observaron signos de hepatotoxicidad en dos pacientes (1,3%) y durante el tratamiento dos pacientes presentaron un aumento de la alanina-aminotransferasa de grado 2 y un paciente un aumento de grado 3 (tasa de incidencia en 10 años de seguimiento 4,2; IC95% 1,4–13,1). No se comunicaron defunciones asociadas con la hepatotoxicidad.
CONCLUSIÓN: En un distrito rural de Malawi, los tratamientos combinados a base de NVP y RMP ofrecieron desenlaces terapéuticos favorables con una buena seguridad toxicológica. Un mayor seguimiento de los pacientes podría ser útil a fin de verificar los efectos a largo plazo de estos tratamientos simultáneos.