Is stopping secondary prophylaxis safe in HIV-positive talaromycosis patients? Experience from Myanmar

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Objectives
The aim of the study was to determine whether it is safe to stop secondary prophylaxis in patients with talaromycosis after immune reconstitution with a sustained increase in CD4 count to ≥ 100 cells/μL after antiretroviral therapy (ART).

Methods
A retrospective cohort analysis was performed in HIV-infected patients treated for talaromycosis between June 2009 and June 2017 in Medical Action Myanmar (MAM) clinics.

Results
Among a cohort of 5466 HIV-infected patients, 41 patients were diagnosed with and treated for clinical talaromycosis. All the patients were on ART and had a CD4 count < 100 cells/μL. Of these 41 patients, 24 patients (71%) were skin smear positive for talaromycosis, while results were negative in 17 patients. Median CD4 count and haemoglobin concentration were 24 cells/μL and 7.7 g/dL, respectively. Seventy-three per cent (30) were male. Among the 41 patients, 11 (27%) died and six (15%) were transferred to other centres. Twenty-four patients (58% of the total diagnosed) stopped itraconazole secondary prophylaxis after starting active ART with CD4 counts > 100 cells/μL for at least 1 year. Throughout the duration of follow-up post itraconazole cessation, the observed incidence of relapse was zero with a total follow-up of 93.8 person-years (95% confidence interval 0–4 per 100 person-years). The median (25th, 75th percentile) duration of follow-up post-prophylaxis discontinuation was 2.8 (2.1, 6.3) years.

Conclusions
Secondary prophylaxis can be safely stopped in patients with talaromycosis after immune reconstitution with a sustained increase in CD4 count to ≥ 100 cells/μL after highly active antiretroviral therapy.

Keywords: HIV, secondary prophylaxis, talaromycosis

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Talaromycosis, a systemic mycosis caused by Talaromyces marneffei, is most commonly found in Southeast Asian countries. It develops most commonly in HIV-positive patients with CD4 counts of ≤ 100 cells/μL. Common clinical manifestations include fever, nonproductive cough, hepato-splenomegaly, weight loss, anaemia, and generalized skin papules with central umbilication. A presumptive diagnosis can be made following the identification of characteristic septate yeast-like organisms under microscopic examination of Wright or Giemsa-stained samples with a sensitivity of approximately 70% [1]. This can be confirmed by culture if facilities are available. Treatment with intravenous amphotericin B for 2 weeks followed by oral itraconazole for 10 weeks is effective and safe but the mortality rate can still be > 25% [2]. Relapse rates as high as 57% were described without itraconazole maintenance therapy in the pre-antiretroviral therapy (ART) era [3]. The optimal duration of antifungal prophylaxis to prevent relapse remains
unclear [4]. Studies reporting the discontinuation of antifungal prophylaxis in HIV-infected patients responding to ART are few and involved small case numbers [5,6,7,8].

Medical Action Myanmar (MAM) is a nonprofit medical organization which operates 10 HIV integrated outpatient clinics for the poor, marginalized and vulnerable population in Myanmar. A retrospective cohort analysis was conducted to determine the relapse rate of talaromycosis after the discontinuation of itraconazole secondary prophylaxis in ART-treated patients between June 2009 and June 2017 in MAM clinics. Diagnosis was clinical with confirmation by Giemsa staining of a skin slit smear from characteristic papular skin lesions where possible. Culture was not available. All patients were treated with amphotericin (0.7 mg/kg/day) for 2 weeks and itraconazole (400–600 mg/day) for 8 to 10 weeks, followed by itraconazole 200 mg as secondary prophylaxis until they had maintained a CD4 count of >100 cells/µL for at least 1 year on ART.

Among a cohort of 5466 HIV-infected patients, 41 patients were diagnosed with and treated for clinical talaromycosis. All the patients were on ART and had CD4 counts <100 cells/µL. Of these 41 patients, 24 patients (71%) were skin smear positive for talaromycosis while results were negative in 17 patients. The median CD4 count and haemoglobin concentration were 24 cells/µL and 7.7 g/dL, respectively. Seventy-three per cent (30%) were male. The demographic and clinical characteristics of skin smear positive and negative patients were similar (Table 1). Among 41 patients, 11 (27%) died and six (15%) were transferred to other centres, from which no clinical data could be obtained. Twenty-four patients (58% of the total diagnosed) stopped itraconazole secondary prophylaxis. The mean CD4 count of discontinued patients was 296 cells/µL, with a maximum of 751 cells/µL and a minimum of 132 cells/µL. Throughout the duration of follow-up post itraconazole cessation, the observed incidence of relapse was zero with a total follow-up of 93.8 person-years (95% confidence interval 0–4 per 100 person-years). The median (25th, 75th percentile) duration of follow-up post-prophylaxis discontinuation was 2.8 (2.1, 6.3) years with a range of 0.5–7.3 years for smear-positive and 1–6.5 years for smear-negative patients.

These findings contribute to the evidence that secondary prophylaxis can be discontinued safely in patients with talaromycosis after immune reconstitution with a sustained increase of the CD4 count to ≥100 cells/µL after highly active antiretroviral therapy.

**Limitation**

As plasma HIV RNA testing was not available in the project, we could not measure HIV RNA at the time of discontinuation and during follow-up.

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**Table 1** Baseline characteristics of talaromycosis patients

| Baseline characteristic | Skin smear positive (n = 24) | Skin smear negative (n = 17) | Patients who had stopped itraconazole prophylaxis (n = 24) |
|-------------------------|-----------------------------|-----------------------------|----------------------------------------------------------|
| Male                    | 17/24 (71)                  | 13/17 (76)                  | 16/24 (67)                                               |
| Age (years)             | 32 (26, 35)                 | 32 (27, 36)                 | 35 (27, 38)                                              |
| Weight (kg)             | 42 (36, 45)                 | 40 (36, 44)                 | 40 (34, 44)                                              |
| CD4 count (cells/µL)    | 23 (14, 38)                 | 27 (14, 38)                 | 27 (14, 39)                                              |
| Haemoglobin (g/dL)      | 7.5 (6.7, 8.9)              | 7.7 (7.0, 9.8)              | 8.2 (6.9, 9.8)                                           |
| ALT (IU/L)              | 35.5 (23.9, 54.1)           | 39.8 (28.0, 53.0)           | 39.9 (29.5, 48.4)                                        |
| Temperature (°C)        | 37.6 (37.3, 38.7)           | 38.1 (37.7, 38.9)           | 37.9 (37.6, 38.7)                                        |
| History of fever        | 20/22 (91)                  | 14/17 (82)                  | 20/24 (83)                                               |
| Lymphadenopathy         | 6/22 (27)                   | 3/12 (25)                   | 5/24 (21)                                                |
| Respiratory symptoms    | 8/24 (33)                   | 5/17 (29)                   | 7/24 (30)                                                |
| Hepatomegaly            | 15/24 (63)                  | 12/17 (71)                  | 16/24 (67)                                               |
| Splenomegaly            | 1/24 (4)                    | 4/17 (24)                   | 5/24 (21)                                                |
| Bone joint pain         | 3/19 (16)                   | 6/15 (40)                   | 5/24 (21)                                                |
| Abnormal CXR            | 13/20 (65)                  | 9/13 (69)                   | 9/24 (38)                                                |
| Duration of ART before diagnosis of talaromycosis (days) | -27 (--40, 11) | -22 (--61, 11) | -19 (--41, 56)                                           |
| Duration of secondary prophylaxis before discontinuation (days) | Not relevant | Not relevant | 346 (267, 456)                                          |
| CD4 count at discontinuation (cells/µL) | Not relevant | Not relevant | 255 (190, 297)                                          |

Values are median (25th, 75th percentile) or n/total (%)

ALT, Alanine aminotransferase; ART, antiretroviral therapy; CXR, Chest X Ray.
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