


Confronting Dual Therapeutic Hurdles in Advanced HIV: A Case Report on INSTIs Resistance and *Talaromyces marneffi* Coinfection

Lun Zou, Yuting Diao, Zhihao Huang, Chunfang You 

Department of Infectious Diseases, Zigong First People's Hospital, Zigong, Sichuan, People's Republic of China

Correspondence: Chunfang You, Department of Infectious Diseases, Zigong First People's Hospital, No. 42, Shangyihao Branch Road 1, Zigong, Sichuan, 643000, People's Republic of China, Email 2421662719@qq.com

Background: Treating patients with human immunodeficiency virus (HIV) integrase strand transfer inhibitors (INSTIs) resistance and concurrent *Talaromyces marneffi* (*T. marneffi*) infection poses a significant clinical challenge, requiring precise antiretroviral adjustments, timely anti-infection, and management of complex drug interactions.

Case Presentation: Interrupted antifungal therapy and INSTIs resistance in an HIV patient coinfecting with *T. marneffi* resulted in severe immunosuppression. Initial voriconazole/imipenem treatment improved peritonitis. However, the symptoms recurred. Antiretroviral therapy (ART) was switched from elvitegravir to zidovudine, lamivudine, dolutegravir, and abacavir. Antifungal therapy adjusted from voriconazole to itraconazole. During the follow-up process, HIV RNA turned negative and the CD4⁺ T cell count increased, but fungal antigens persisted until the 10-month follow-up period.

Conclusion: This case emphasizes genotype resistance testing-guided ART modification and rigorous opportunistic infection management in drug-resistant HIV patients. Coordinated care and timely interventions can enhance the outcomes in high-risk cases.

Keywords: HIV/AIDS, integrase strand transfer inhibitors, *T. marneffi*, drug resistance, treatment

Introduction

Integrase strand transfer inhibitors (INSTIs) are a class of anti-human immunodeficiency virus (HIV) drugs with a high genetic resistance barrier, making them a preferred option for antiretroviral therapy (ART).^{1,2} However, increasing INSTIs resistance threatens the efficacy of ART, particularly in regions with limited access to drug resistance testing and as evidenced by recent surveillance data from China.³ *Talaromyces marneffi* (*T. marneffi*) is an opportunistic pathogen that poses a significant threat to human health, particularly in Southeast Asia. This fungus is known to cause disseminated infections, especially in immunocompromised individuals such as those with HIV infection, particularly in those with advanced immunosuppression (for example, CD4⁺ T cell count below 200×10⁶ /L) in endemic regions.⁴ In clinical practice, the management of patients with INSTIs resistance, especially when combined with other infections such as *T. marneffi*, remains complex. Co-treatment with HIV and *T. marneffi* can complicate the management of drug resistance due to potential drug-drug interactions and overlapping toxicities.⁵ The limited experience in treating patients with both INSTIs resistance and *T. marneffi* infection necessitates ongoing surveillance, and research into management strategies is essential to maintain their efficacy and improve patient care. This paper reports a case of HIV infection with both INSTIs resistance and *T. marneffi* infection, and demonstrates the challenging process of drug combination therapy.

Case Presentation

A 30-year-old male was admitted to our hospital on July 13, 2023, with abdominal pain and fever for one day, accompanied by nausea and vomiting. The patient had a history of HIV infection combined with *T. marneffi* infection two years prior. The patient received ART with elvitegravir and without regular follow-up. He was administered



amphotericin B followed by voriconazole for antifungal treatment, but discontinued after one month. Physical examination revealed tenderness and rebound pain around the umbilicus and the right abdomen. The patient had a history of unprotected homosexual deeds and no other underlying disease.

Laboratory tests showed that C-reactive protein (217.8 mg/L), interleukin-6 (105.3 pg/mL), serum amyloid protein (332.9 mg/L), procalcitonin (0.455 µg/L), 1,3-β-D-glucan test (G test) (120.984 pg/mL) and galactomannan test (GM test) (8.112 S/CO) levels increased, while the CD4⁺ T cell count (43×10^6 /L) and CD4⁺/CD8⁺ T cell ratio (0.25) decreased. The HIV RNA level was 1.25×10^5 copies/mL. Serum amylase and lipase levels did not increase. Interferon-gamma release assay result was negative. The *T. marneffei* antigen was positive. HIV genotypic resistance testing revealed INSTIs resistance. Abdominal computed tomography scan demonstrated inflammatory alterations that were indicative of peritonitis. Therefore, the patient was diagnosed with HIV and *T. marneffei* coinfection, and intravenous antifungal therapy with voriconazole was administered for 14 days. Empirical imipenem/cilastatin was initiated for broad-spectrum coverage of potential bacterial co-infection. Subsequently, his symptoms improved and the levels of inflammatory markers, G test result and GM test result decreased. The patient was discharged on July 30. The anti-HIV regimen was adjusted to zidovudine and lamivudine (AZT/3TC) combined with lopinavir/ritonavir (LPV/r) guided by the genotypic resistance results, and the antifungal regimen was adjusted to itraconazole based on the drug-drug interactions.

Unfortunately, on August 16, 2023, the patient was hospitalized again because of abdominal pain. The levels of inflammatory markers and fungal antigen increased again. C-reactive protein was 178.8 mg/L and procalcitonin was 0.061 µg/L, respectively. The G test result was 63.708 pg/mL and the GM test result was 6.541 S/CO. The CD4⁺ T cell count (88×10^6 /L) and CD4⁺/CD8⁺ T cell ratio (0.57) were slightly higher than those at the previous admission. Imaging examination by abdominal computed tomography scan suggested intraperitoneal and retroperitoneal inflammatory reactions. The patient was then treated with voriconazole and imipenem/cilastatin. As the symptoms improved and the inflammatory response was controlled, the patient was discharged on August 25. The anti-HIV regimen was adjusted to AZT/3TC, dolutegravir and albuviride (albuviride for 3 months), considering the efficacy of ART and drug-drug interactions. The patient was treated with oral voriconazole as antifungal therapy after discharge.

Four months after the first admission, the patient did not experience any further abdominal pain. HIV RNA was undetectable and the CD4⁺ T cell count increased to 119×10^6 /L. However, *T. marneffei* antigen, the G test (162.848 pg/mL) and the GM test (6.920 S/CO) were still positive. The patient continued the current treatment regimen. Ten months after the first admission, the *T. marneffei* antigen and G test result turned negative, and the CD4⁺ T cell count further increased to 143×10^6 /L. However, the GM test result (8.585 S/CO) remained positive. The antifungal regimen was changed to a prophylactic treatment with itraconazole. The ART regimen was then continued. The laboratory test results and drug administration process throughout the patient's treatment history are summarized in Figure 1.

Discussion

In this report, we described an INSTIs-resistant HIV case with *T. marneffei* coinfection. Due to HIV genotypic resistance, opportunistic infection, and drug-drug interactions, the choice of treatment options was extremely challenging.⁶ The management of advanced HIV infection complicated by the dual challenges of INSTIs resistance and *T. marneffei* coinfection represents a critical yet understudied clinical scenario, as illustrated in this case. This discussion highlights the importance of tailored therapeutic strategies to achieve favorable outcomes.

The optimization of ART regimens in the face of drug resistance is further complicated by the need to balance efficacy, safety, and patient adherence. The WHO-recommended first-line ART regimens, which include a combination of efavirenz, tenofovir disoproxil fumarate, and lamivudine or emtricitabine, have been widely used.⁷ However, some evidence of pre-existent drug resistance has been observed, suggesting the need for careful screening before first-line ART options.^{8,9} This is particularly relevant in regions with high treatment coverage, where the emergence of drug-resistant strains can undermine treatment success.¹⁰ Post-resistance ART strategies are crucial for managing patients who have developed resistance to their current regimens. The implementation of adherence interventions has been shown to result in virologic resuppression in a substantial number of patients with an initial elevated viral load, thereby avoiding unnecessary regimen changes.¹¹ Additionally, the use of novel agents and optimized background regimens can provide effective treatment options for those with multidrug-resistant HIV.¹²

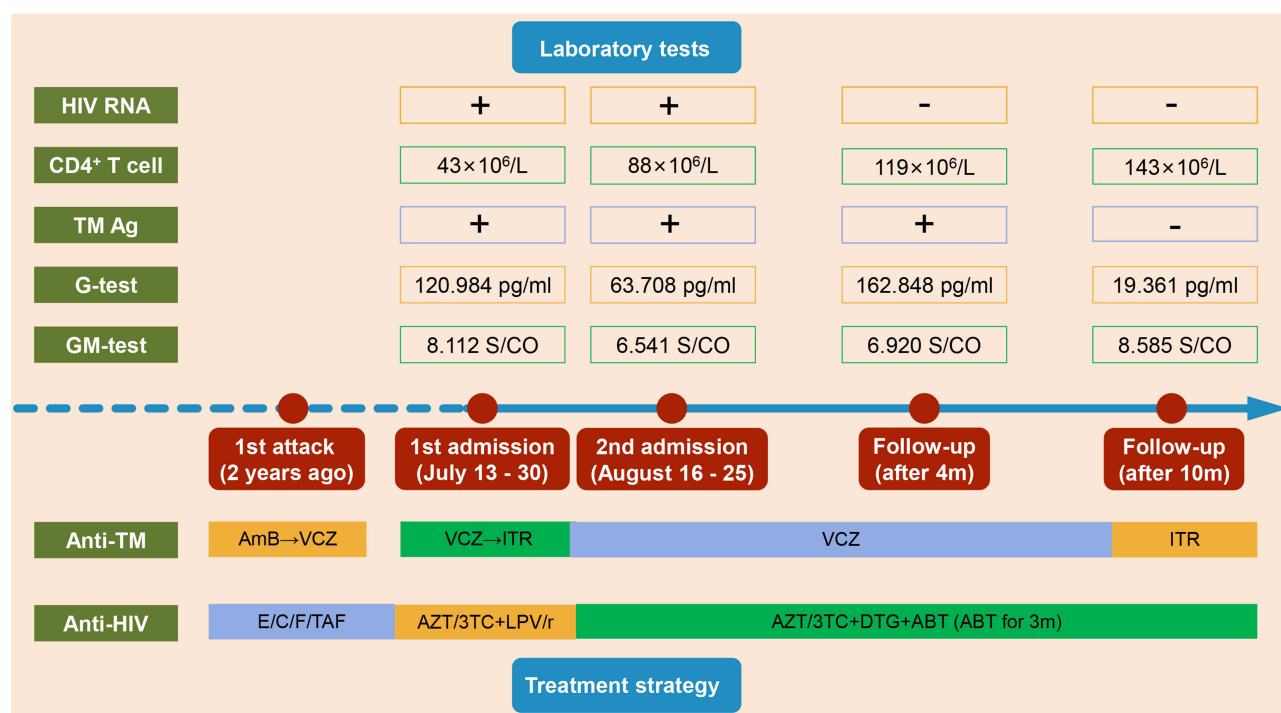


Figure 1 The laboratory tests and drug administration process throughout the patient's treatment history.

Abbreviations: ABT, albuviridine; Ag, antigen; AmB, amphotericin B; AZT/3TC, zidovudine and lamivudine; DTG, dolutegravir; E/C/F/TAF, elvitegravir; G test, 1,3-β-D-glucan test; GM test, galactomannan test; HIV, human immunodeficiency virus; ITR, itraconazole; LPV/r, lopinavir/ritonavir; RNA, ribonucleic acid; TM, *Talaromyces marneffei*; VCZ, voriconazole.

INSTIs are cornerstone agents in modern ART because of their high genetic barrier to resistance and potent viral suppression. However, emerging reports of INSTIs resistance, particularly in regions with limited access to routine resistance testing, threaten their long-term utility.^{3,13} In this case, the patient developed resistance to INSTIs, manifested by failure of the elvitegravir-containing regimen, likely because of suboptimal adherence and irregular follow-up. Resistance mutations in the integrase gene may have arisen during periods of incomplete viral suppression, underscoring the importance of adherence counseling and viral load monitoring. The subsequent switch to dolutegravir, a second-generation INSTIs with a higher resistance barrier, combined with the fusion inhibitor albuviridine, successfully restored the virologic control. Dolutegravir was prioritized over other INSTIs due to its proven activity against the detected resistance mutations. This aligns with evidence supporting dolutegravir-based regimens as salvage therapy for INSTIs-resistant cases, especially when combined with agents from other drug classes to circumvent cross-resistance.^{14,15} Nevertheless, the rising prevalence of INSTIs resistance calls for expanded access to genotypic resistance testing and education on adherence in resource-limited settings.

T. marneffei, endemic to Southeast Asia, is a life-threatening opportunistic infection in advanced HIV. Coinfection with *T. marneffei* is associated with a high mortality risk in HIV-infected patients regardless of CD4⁺ T cell count.¹⁶ This patient's recurrent *T. marneffei*-related peritonitis, despite initial antifungal therapy, highlighting the challenges of managing disseminated *T. marneffei* in the context of delayed immune recovery. The transient response to voriconazole and subsequent relapse may reflect subtherapeutic drug levels due to poor absorption, drug-drug interactions with ART, or antifungal resistance.^{5,17} Notably, the prolonged time to *T. marneffei* antigen clearance (10 months) emphasizes the need for extended antifungal courses, particularly in patients with persistent immunosuppression. Delayed immune reconstitution (CD4⁺ T cell count increasing from 43×10⁶ /L to 143×10⁶ /L over 10 months) likely contributed to the gradual resolution of *T. marneffei* infection, reinforcing the critical role of ART in restoring pathogen-specific immunity. However, persistently elevated GM test results suggest residual fungal antigenemia, warranting long-term antifungal prophylaxis with itraconazole to prevent relapse.

The management of HIV and *T. marneffei* coinfection requires careful balancing of drug interactions, resistance profiles, and immune recovery. Voriconazole, a CYP2C19/CYP3A4 substrate, interacts with ritonavir-boosted protease inhibitors (eg, lopinavir/ritonavir) due to CYP3A4 inhibition, necessitating dose adjustments or switches to alternatives like itraconazole.^{18,19} However, in cases of severe infection or treatment failure, voriconazole may be reintroduced alongside ART regimen optimization, such as using dolutegravir, an integrase inhibitor with minimal CYP450 interactions, and retained efficacy against INSTIs resistance mutations.²⁰ Amphotericin B remains the gold standard for severe disseminated infections, while voriconazole or itraconazole are preferred for maintenance therapy, guided by fungal biomarkers and CD4⁺ T cell recovery.⁶ Prolonged antifungal prophylaxis is often required until immune restoration, emphasizing the synergy between viral suppression and fungal clearance.^{21,22}

Conclusions

This case highlights the importance of tailored therapeutic strategies to achieve favorable outcomes in the context of ART resistance, opportunistic *T. marneffei* infection and drug-drug interactions. Successful management requires genotype-guided ART optimization, extended *T. marneffei* antifungal therapy monitored by GM/G biomarkers until immune recovery, and strategic avoidance of drug-drug interactions.

Data Sharing Statement

The patient data used in this study are partially presented in the paper. The remaining data are available upon reasonable request by contacting the corresponding author.

Ethics Approval and Informed Consent

Ethical approval for this case report (Approval Number: 2024136) was obtained from the Ethics Committee of Zigong First People's Hospital, Sichuan, China and complied with the Declaration of Helsinki as revised in 2013. Written informed consent was obtained from the patient for publication of the case report.

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Disclosure

The authors report no conflicts of interest in this work.

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