

Retinal toxicity with Ritonavir

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Dear sir,

Non-systemic, ocular toxicity caused by medications used in highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) infection is an uncommon adverse event ^[1]. Roe *et al* ^[2] reported Ritonavir associated retinal pigment epitheliopathy in three patients. We report a patient on Ritonavir for seven years who presented with decreased vision concomitantly with mild liver dysfunction. Outer retinal abnormalities were seen on spectral-domain optical coherence tomography (SD-OCT) that markedly improved within two weeks of discontinuation of Ritonavir. No abnormalities were seen on fundus autofluorescence (AF) and fluorescein angiogram (FA). The study was approved by institutional review board by New Jersey Medical School, University of Medicine and Dentistry of New Jersey (merged into Rutgers University in 2012).

A 47-year-old HIV-positive man was referred to our institution for progressive visual loss and central relative scotoma for two weeks in the left eye. His past medical history included HIV infection (for 7y), hypothyroidism, and hypercholesterolemia. He denied any history of tobacco or alcohol abuse. The CD4+ T-cell count was 438 cells per microliter with undetectable HIV-1 RNA. He had no history of AIDS-defining diseases. He had been on the HAART therapy for 6y since the diagnosis of HIV which included Epzicom (abacavir + lamivudine) 600 mg/300 mg daily, Lexiva (fosamprenavir) 1400 mg daily, and Norvir (Ritonavir) 200 mg daily. Mild liver dysfunction was seen two months before visual symptoms started: increased aspartate aminotransferase (AST) at 51 U/L (normal <40 U/L). Abnormal lipid profile had also been noted in the previous 3mo: elevated serum cholesterol (268 mg/dL; normal

<200 mg/dL), and decreased high-density lipoprotein (HDL) (48 mg/dL; normal >55 mg/dL).

On examination, the best corrected visual acuity (BCVA) was 20/25 in the right and 20/400 in the left eye with a central scotoma confirmed by confrontation visual field exam. Anterior exam of both eyes was normal without any uveitis or vitritis. Posterior segment examination revealed a 400- μ m circular, slightly hyperemic lesion centered at the left fovea (Figure 1A). SD-OCT revealed thickened and irregular retinal pigment epithelium (RPE) with overlying loss of inner/outer segment junction layer (IS/OS) integrity in the foveal area; the external limiting membrane (ELM) was intact but slightly irregular (Figure 2A). The AF showed no abnormalities. The FA showed no hypo- or hyperfluorescence in the foveal area or elsewhere. Possibility of Ritonavir ocular toxicity was suspected in light of recent liver abnormalities; Ritonavir has hepatic clearance. Ritonavir was discontinued immediately after consulting his infectious disease physician. BCVA (Snellen) improved from 20/400 to 20/25 within 2wk. Humphrey visual field (HVF) showed a smaller central scotoma with a mean deviation (MD) of -3.79 ($P < 0.02$) (Figure 3). The macular examination showed resolution of the foveal hyperemic lesion (Figure 1B). OCT of the macula improved; RPE layer had normalized with less disrupted and smoother IS/OS layer and a normal ELM (Figure 2B). The results of laboratory work-up 2-week later revealed rapid plasmin reagan (RPR) titer 1:64 confirmed with a reactive fluorescent treponemal antibody absorption (FTA-Abs), erythrocyte sedimentation rate (27, 0-10 mm/h), negative Bartonella antibody panel, toxoplasma IgM and IgG antibody titers and a normal chest X-ray. On the basis of positive syphilis titers, intravenous penicillin treatment was initiated (this was 3wk after Ritonavir was stopped and improved visual acuity was documented to 20/25 and marked improvement of OCT was documented before the syphilis treatment was initiated). Subsequent visits showed improvement in macular exam, and on HVF. OCT was normal with well-defined IS/OS layer and ELM (Figure 2C) 6wk after Ritonavir was discontinued. Follow-up visit 6mo later revealed, BCVA of left eye stable at 20/25 with a normal macular exam, AF, FA and OCT.

The patient presented with retinal pigment epitheliopathy which was attributed to Ritonavir toxicity in the presence of abnormal liver function tests (LFTs). The epitheliopathy resolved within 2wk of discontinuation of Ritonavir. Syphilis titers were reported to be positive and penicillin treatment was

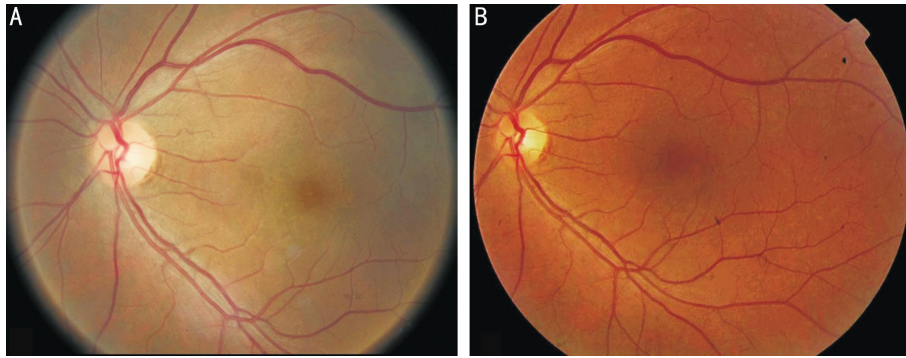


Figure 1 Color fundus photographs of the left eye at presentation (A) and 2wk after discontinuation of Ritonavir (B).

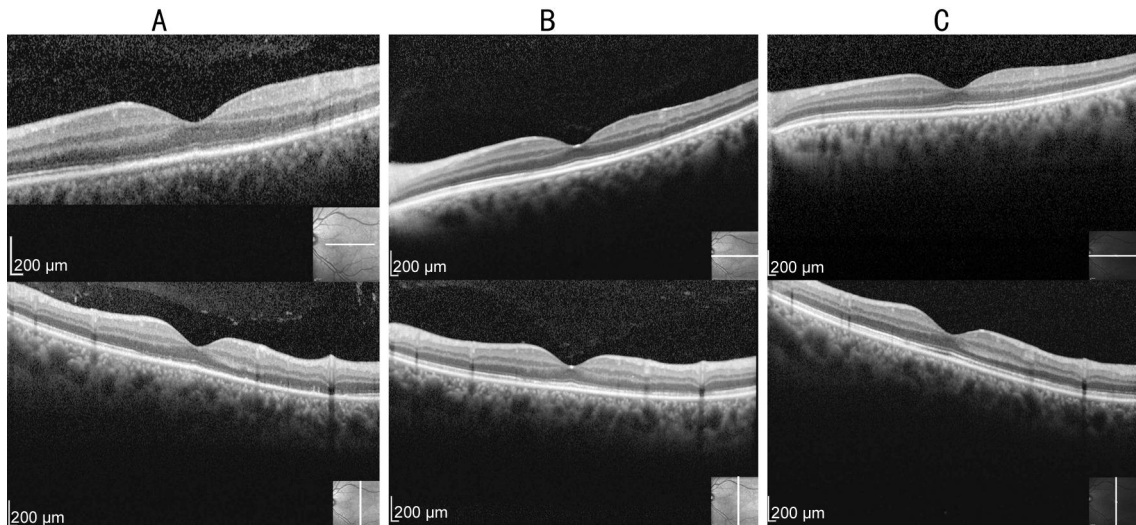


Figure 2 SD-OCT examination of the left eye at presentation (A), 2wk after discontinuation of Ritonavir (B), and 6wk after discontinuation of Ritonavir (C).

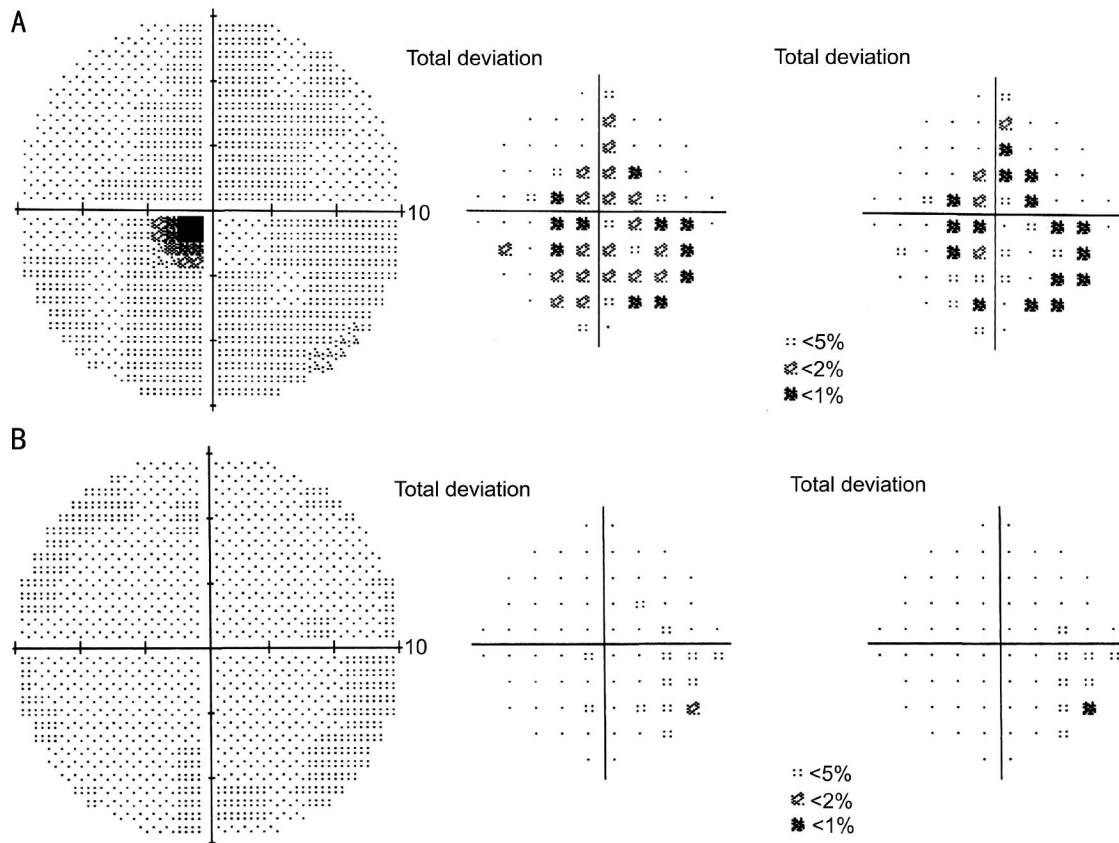


Figure 3 HVF examination of the left eye 2wk (A) and 4wk (B) after discontinuation of Ritonavir.

initiated 3wk after discontinuation of ritonavir. Posterior placoid chorioretinitis has been reported with syphilis^[3]; however, we do not believe the macular findings in our patient were syphilis related, in light of improvement in clinical examination, visual acuity to 20/25 and SD-OCT before the syphilis treatment was started; Ritonavir is more likely to be the culprit. Also, the FA of our patient lacked the typical late staining that is noted with placoid chorioretinitis^[4]. Roe *et al*^[2] recently reported three cases of retinal pigment epitheliopathy in HIV-positive patients receiving Ritonavir. Ritonavir is 99% protein bound and metabolized in the liver through cytochrome P-450 pathways. Ritonavir toxicity is dose-related. It was showed that even a moderate liver impairment would double its serum level^[2]. It is prudent to believe mild liver dysfunction 2mo prior to ocular symptoms in our patient would be the triggering event which caused Ritonavir serum levels increased to Ritonavir toxic level; even though it had been well tolerated for the previous six years. In contrast to three patients in Roe *et al*'s report^[2], RPE changes in our patients were unilateral, mild and transient. It may be a reflection of an early diagnosis of RPE

toxicity in our case such that the changes were reversible with a rapid improvement in visual acuity and clinical findings with discontinuation of the drug.

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