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RETINAL IMPAIRMENT ASSOCIATED WITH LONG-TERM USE OF RITONAVIR AMONG HIV PATIENTS: A SYSTEMATIC REVIEW FOR PRIMARY EYE CARE PRACTICE

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ABSTRACT

Introduction: *Ritonavir as part of Highly Active Antiretroviral Therapy (HAART) is a potent inhibitor of HIV protease that have been reported causing retinal impairment in the long term use. Primary eye care (PEC) is an integral part of primary health care that provides an early screening for drug induced retinal toxicity, by using a funduscopy examination. This study proposed to review and analyze some case reports conducted on long-term use of ritonavir that affects retinal impairment among HIV patients, in primary eye care practice.*

Method*: PubMed and Google Scholar were used to perform a systematic review of retinal impairment associated with long-term use of ritonavir among HIV patients. Using PRISMA 2020 Guidelines, nine case reports and one case series were included in this review and only focus on simple funduscopic examination for primary eye care practice.*

Result*: Funduscopy mainly showed bilateral Retinal Pigment Epithelium (RPE) atrophy with hypertrophy or mottling. Two cases found bilateral crystalline deposits with pigment disruption. One case showed rounded hypopigmented lesion. Bilateral subtle annular pattern of RPE was found in one case. Bilateral retinitis pigmentosa-like appearance found in one case while another found unilateral hyperemic lesion at the left fovea.*

Conclusion*: Retinal impairment detected on funduscopy occurred in HIV patients on long-term use of ritonavir.*

Keywords: Ritonavir, Retinal Impairment, HIV, Primary Eye Care

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INTRODUCTION

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Retinal impairment that associated with long-term use of Ritonavir as antiretroviral therapy for HIV patients is uncommonly reported. Ritonavir is an inhibitor of the human immunodeficiency virus type 1 (HIV-1) protease and is now used in combination in highly active antiretroviral therapy (HAART). The adverse effects of Ritonavir may cause disadvantageous on the eyes, especially on the retina. Rare cases of retinopathy have been reported in the literature since 2011 with heterogeneous phenotypes ranging from macular atrophy, intraretinal cysts, macular telangiectasia[4] to retinitis pigmentosa-like presentation[5] in the long term use of ritonavir.

Primary eye care (PEC) is a facility which accessible and give comprehensive care for patients' eye care treatment in a competent manner. PEC provides the patient with the first contact for eye care as well as a lifetime of continuing care[6]. PEC is the primary health care (primary health care) to help undertake the prevention of eyes diseases which some lead to blindness and it should be a vital part of PHC. The ophthalmologist is certainly suitable and cost-effective provider of PEC[6]. Although in some conditions, PEC can be provided by general practitioners at basic health units and rural health centers[8] with limited resources.

We conducted a systematic review of the published case and serial case reports describing the clinical features associated with ritonavir-induced retinal toxicity. In this review, we focus on PEC practice to diagnosing the effect of HAART use earlier.

HIV Associated with Retinopathy

A. Pathophysiology

Human Immunodeficiency Virus (HIV) are divided into two types, HIV-type 1 (HIV-1) and HIV-type 2 (HIV-2), the main agent of AIDS is HIV-1[9]. The pathogenesis of HIV infection and the progression to AIDS are a result of the infecting virus isolate and the host's immune response to the virus[9]. HIV is able to enter the body via intact mucous membranes, eczematous or injured skin or mucosa and by parenteral inoculation. HIV attaches first to dendritic cells or macrophages/monocytes. HIV is taken by macrophages and replicated as shown for M cells in the mucosa[11].

After a day or two the virus can be detected in regional lymphatic tissue and within 5–6 days in regional lymph nodes. After 10–14 days post-infection HIV can be detected in the whole body, including the nervous system[11]. Most of the infected individuals present symptoms resembling flu-like illness, as fever, pharyngitis, oral ulcers, lymphadenopathy, arthralgia, myalgia, weight loss, and malaise. During acute HIV-1 infection, the number of CD4+ T-cells dramatically declines before the onset of antiviral immune response[9].

B. HIV Retinopathy

The eye is infected to HIV virus either directly or indirectly by numerous opportunistic infections. HIV retinopathy is an ocular affection occurring especially in HIV positive patients with deep immunodeficiency. HIV-related ophthalmic manifestations are extensive and may affect any part of eye. Dry eye and HIV retinopathy were the most common ocular manifestations found in patients[12]. In the pre-HAART era, CMV retinitis was the most common HIV-associated retinopathy that occurred in 20%-40% of patients. CMV retinitis occurs only after CD4 T lymphocyte counts drop below 50 cells/uL. If left untreated CMV retinitis leads to retinal necrosis that may result in rhegmatogenous retinal detachment (RD) in three to six months of diagnosis.

Ritonavir Overview

A. Ritonavir Profile

Ritonavir as a part of HAART acts as a potent inhibitor of HIV protease[4]. Ritonavir prevents the cleavage process of viral polyprotein precursors into mature and functional proteins, hence interrupting the production of new viral particles[14]. The inhibition of HIV protease results in the release of immature non-infectious virions that halt the spread of the virus to uninfected cells. Ritonavir has been shown to be 98% to 99% protein-bound, and its primary site of metabolism is in the liver.

B. Side Effect

The most common side effects found in patients with ritonavir treatment are general weakness, peripheral paresthesia, nausea, vomiting, diarrhea, rash, and fatigue, and

with long-term use it's possible to find hyperlipidemia and lipodystrophy. Visual symptoms are rare but have been reported in some studies that described the long-term effects of protease inhibitors, including ritonavir, in HIV-positive[4]. Visual change can be detected and identified by eye examination such as funduscopy Fundus Autofluorescence (FAF), Fluorescein Angiogram (FA), Spectral Domain-Optical Coherence Tomography (SD-OCT), Electroretinogram (ERG), and Humphrey Visual Field.

included as a competence that must be achieved at the time of graduation as a doctor[16] although in fact not all general practitioners are able to perform funduscopy due tu limited resources. Therefore general ophthalmologists must also emphasize this for early detection of retinal toxicity on HIV patients. Fundus examination showed hypopigmented annular lesions in the macular region corresponding to the retinal pigment epithelium (RPE) atrophy[1,3-4,17-20] and parafoveal opacification in the macula[4] **(Figure 1.)** corresponding to the crystal and pigment deposit[15]

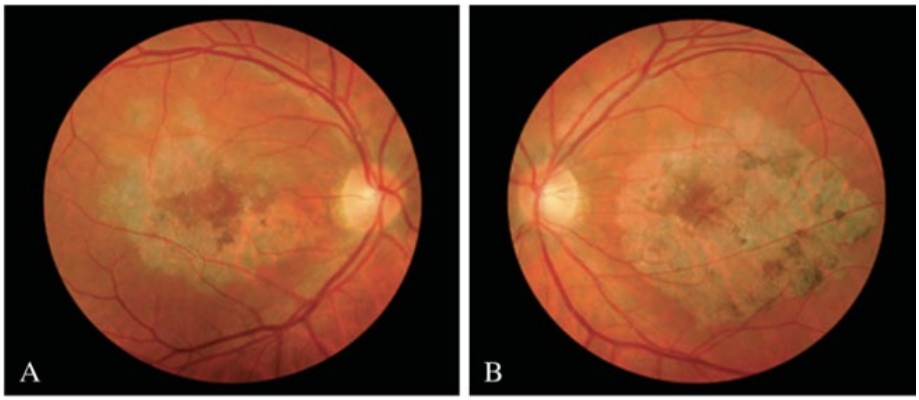

Figure 1**. Fundus photograph: hyperthrophic and atropic changes in the RPE in macula as well as parafoveal opasification[4]**

In Indonesia, based on Standar Kompetensi Dokter Indonesia (Indonesian Doctor Competency Standars) 2019, general practitioners must be able to do funduscopy independently. Funduscopy is

(Figure 2.) Some studies also showed scattered bone spicule-like pigment changes on the mid-peripheral retina[5] and slightly hyperemic lesion centered at the fovea[21] **(Figure 3.)**

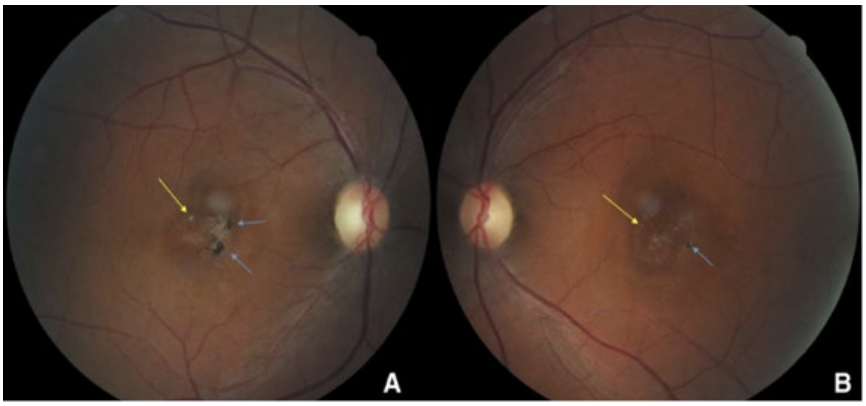

Figure 2. **Fundus photograph: crystalline (yellow arrow) and pigment deposits (blue arrow) in the macula[15]**

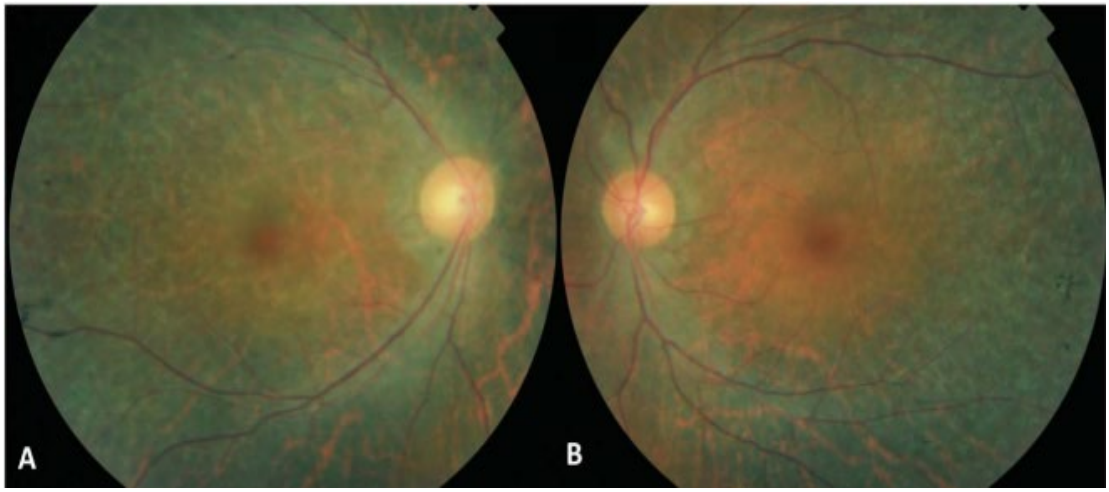

Figure 3**. Fundus photograph: scattered bone spicule-like pigment changes on the mid-peripheral retina[5]**

METHODS

A. Study Selection

PubMed and Google Scholar were used to conduct a literature review. We searched for case report studies that evaluate the effect of ritonavir on the retina. The search query included ritonavir AND (retina OR retinal OR ocular) AND (toxicity OR impairment OR damage). The following were the inclusion criteria for each study: (1) documented retinal impairment due to ritonavir treatment, (2) conducted in human eyes, and (3) published in the last 10 years. We adhered to the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. **(Figure 4.)** All the reports were critically appraised by 3 independent reviewers based on Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Report.

B. Study eligibility criteria

The population-intervention-comparator-outcomes-study design (PICOS) framework was used to identify eligible cases, as follows:

- Population. Only human patients, with no restrictions on age or other demographics
- Intervention and comparator. Long-term use of Ritonavir on HIV patients. We excluded the drug combinations used. No comparator was required.
- Outcomes. Retinal impairment showed on eye examination. In this study, we limit the examination on funduscopy which mostly primary health care had.
- Study design. We included only case reports and case series published in full text.

Based on WHO-UMC Causality Assessment System, long-term use of ritonavir categorize into "possible" cause to retinal impairment that showed by abnormality on funduscopic examination with reasonable time relationship to drug intake, but it might also be explained by patient's underlying disease or other drugs that patients already take. In this case, rechallenge was not necessary because discontinuation or interruption of ritonavir as part of HAART may result in viral rebound, immune decompensation, and clinical progression which can harm patients.

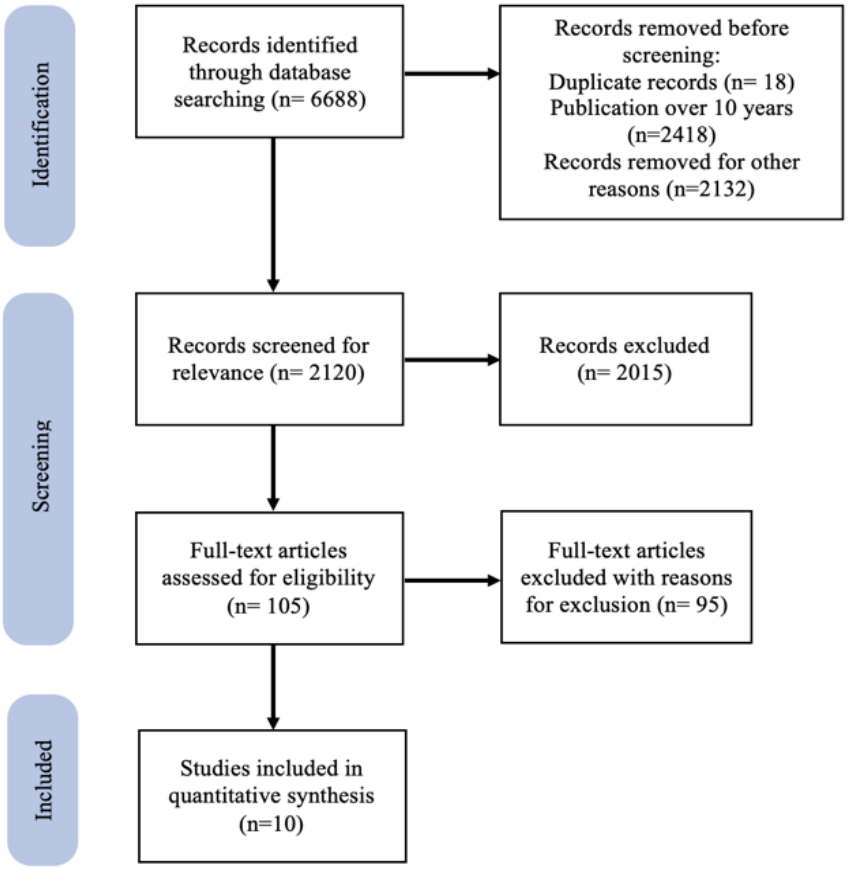

Figure 4. **Flow diagram of the study selection process**

After assessing studies for risk of bias using Cochrane risk-of-bias tool, we found no risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, and incomplete outcome data. However there is an unclear risk of bias for blinding of outcome assessment since there is a difference between the Ritonavir dose taken by participants and half of the studies didn't include the Ritonavir dose. We used subgroup analysis to explore possible causes of heterogeneity among study results.

RESULTS

The literature search identified total of 10 case reports. From the 10 case reports which were included in this review, 9 of them were single case reports and 1 was a case series including 3 patients. Ritonavir was administered ranging from 100 mg daily or twice daily but few reports didn't state the dose taken by the patients. The patients were all male and the mean age of the patients was 41 years, ranging from 30-59. The overall average treatment duration was 93 months, ranging from 19 to 216 months treatment duration. Some authors included the presence of liver dysfunction.

Our outcome is to find retinal impairment showed on eye examination in HIV patients. In this study, we limit the examination on funduscopy which mostly primary health care have to visualize the retina. As described, the retinotoxicity mostly presented in bilateral macular, while 3 cases presented in bilateral retinal and macular[1,5,19], and 1 case only involved in unilateral macular[21].

Funduscopy examination mainly showed bilateral RPE atrophy with hypertrophy or mottling. Two cases found bilateral crystalline deposits with pigment disruption. Bilateral subtle annular pattern of retinal RPE was found in one case. Another author found bilateral retinitis pigmentosa-like appearance of the fundus with scattered bone specula pigmentation. Tu et al. found unilateral hyperemic lesion centered at the left fovea.

To monitoring the further implication of ritonavir treatment, some authors reported the follow-up examination ranging from 6 to 24 months. Some authors reported the follow-up examination of the ritonavir side effect. Roe and Biancardi et al report the decreasing of visual acuity with significantly larger RPE hypertrophy and atrophy after 24 and 8 months of follow-up. Some reported the bilaterally stable of visual acuity and clinical appearance of the patients after cessation of ritonavir, in nearly or more than 24 months[1,15] and 6 months[21] of follow-up.

DISCUSSION

We have concluded some publication suggested that ritonavir causes retinotoxicity. However, there are some limitation of the evidence included in the review which are not explained on all the publication, such as the doses of drugs and abnormalities finding after several period of follow-up time.

Roe et al. published the first case series in 2011 describing retinal anomalies in HIV-positive individuals treated with ritonavir. They documented three patients with varying degrees of bilateral macular RPE atrophy, macular telangiectasia, cystic gaps, and parafoveal intraretinal crystals[4]. It's worth noting that these three individuals, like another instance by Louie, Bunod, and Tu, had a history of liver dysfunction[1,3,21]. Because ritonavir is predominantly removed through the hepatobiliary system in humans, it's probable that liver failure in these patients inhibited ritonavir removal, resulting in higher circulating drug levels[5].

Table 1. **Result**

Authors	Number of patients	Sex	Age	Ritonavir dose	Treatment duration (m)	Liver dysfunction	Retinal involvement	Funduscopy	Follow-up period duration (m) and findings
Bunod et al.	1	M	47	Not stated	216	Absent	Bilateral macular	Bilateral macular atrophy	-
Non et al.	1	M	36	Not stated	156	Present	Bilateral macular	Bilateral RPE atrophy with RPE mottling	-
Roe et al.	3	M	46; 45; 40	100 mg twice daily	19; 30; 60	Present	Bilateral macular	RPE hypertrophy and atrophy were seen in the macula of each eye; Loss of foveal transparency; Intraretinal crystalline deposits	24 m; decreased visual acuity; RPE hypertrophy and atrophy in macula were significantly larger; Bilateral intraretinal crystals
Pinto et al.	1	M	30	Not stated	60 (24 m interruption)	Absent	Bilateral macular	Discrete perimacular ring of pigment mottling OU	-
Biancardi and Curi	1	-	-	Not stated	Long term (not specified)	-	Bilateral macular	Rounded hypopigmented lesions surrounded by numerous small lesions; RPE atrophy	8 m; Reduction of background granularity and hyper-AF pattern and increase in hypo-AF areas of RPE atrophy
Faure et al.	1	M	49	100 mg twice daily	120	Absent	Bilateral macular	Bilateral crystalline maculopathy in conjunction with pigment disruption.	Nearly 24 m; Patient clinically stable after ritonavir cessation; Further remodelling with newly found pattern of pigment deposits
Louie and Jones	1	M	53	100 mg daily	84	Present	Bilateral retinal and macular	Bilateral subtle annular pattern of retinal RPE around the fovea	More than 24 m; Bilateral stable visual acuity, clinical appearance, visual field testing, and OCT
Mesquita et al.	1	M	53	Not stated	120	Absent	Bilateral retinal and macular	Diffuse bilateral RPE atrophy	-
Papavasileiou et al.	1	M	59	100 mg daily	96	Absent	Bilateral retinal and macular	Bilateral retinitis pigmentosa-like appearance of the fundus with scattered bone specula pigmentation	-
Tu et al.	1	M	47	200 mg daily	84	Present	Unilateral macular (LE)	Unilateral (LE) hyperemic lesion centered at the left fovea	6 m; BCVA of left eye stable at 20/25 with a normal macular exam, AF, FA and OCT

Another possible factor determining the degree of retinal damage, in addition to the length of exposure to the medication, is its serum concentration. This was observed in investigations by Tu et al and Pinto et al, implying that hepatic lesions in ritonavir users would raise the compound's serum levels, increasing the risk of retinal damage and aggravation. After stopping ritonavir, one patient's visual acuity improved, according to Tu et al[17,21].

Ritonavir toxicity studies in mice, rats, and dogs were undertaken. The liver and retina were the main organs targeted. Repeated high oral doses of ritonavir cause phospholipidosis in rodents, resulting in retinal degeneration and hypertrophy of the retinal pigment epithelium, as seen in histology and electron microscopy examinations of amorphous granular inclusion bodies in the liver and retina. With higher liver enzymes, the phospholipidosis was more pronounced in the retina than in the liver. Phospholipidosis is a typical occurrence following the treatment of amphiphilic cationic drugs that may alter phospholipid metabolism[22].

All studies of persistent ritonavir toxicity have a few clinical symptoms in common. Pigmentary alterations in the macula are a common finding[4-5,15,17-21]. A granular appearance of the retinal pigment epithelium in the macula has been documented in several cases[5,15,18], few in a bull's-eye pattern[20,22] and others with a less particular pattern of pigment defects[3-15,18-19,21]. Non et al. and Pinto described a bull's-eye pattern that included retinal epithelial alterations, macular atrophy, and annular macular pigmentation, which looked similar to bull's eye maculopathy, a condition traditionally associated with chloroquine toxicity[17,21].

According to a study by Papavasileou et al, ritonavir can simulate retinitis pigmentosa. Retinopathy phenocopying retinitis pigmentosa can be caused by a variety of causes (pseudoretinitis pigmentosa). It's critical to distinguish these illnesses from RP since, unlike RP, these conditions are usually curable[5].

Ritonavir-related retinal toxicity appears to arise only after long-term use[4-5,15,17-21]. In documented cases, the shortest period of therapy before diagnosis was 19 months. This case's 7-year history of ritonavir use before to diagnosis is consistent with earlier accounts. The loss of vision caused by this toxicity can be worse[4,15,19,21], and there have been reports of advancement even after the medicine has been stopped. Early detection and withdrawal of ritonavir use are critical, as one case was reported to be reversible in a patient with acute and symptomatic illness[21].

Furthermore, Vadlapatla et al. discovered that ritonavir inhibits hypoxia-inducible factor 1 (HIF1) and vascular endothelial growth factor (VEGF) in retinal pigment epithelial cells in vitro. Inhibition of VEGF causes choriocapillaris and photoreceptor degradation in nonhypoxic mice's retinas[23]. VEGF may also have a direct neurotrophic effect on photoreceptors, according to Kurihara et al. As a result, it's possible that ritonavir's persistent reduction of VEGF synthesis could deplete neurotrophic factors important for photoreceptor health or create choriocapillaris vascular malfunction, affecting both the retinal pigment epithelium and the photoreceptors[24].

Needless to say, further study is indicated to better characterize the pathophysiology of this toxicity.

CONCLUSION

Despite the fact that case studies discussing ritonavir's adverse effects on the retina have been rare in the last decade, we continue to elaborate on those reports comprehensively.

This systematic review summarizes findings of retinal toxicity alterations related with long-term ritonavir usage. It might be beneficial to raise primary eye care practitioners' awareness of the importance of early diagnosis of sight-threatening side effects associated with HIV patients' ritonavir therapy, so that they can refer to a retina specialist for further medical examination and research to gain a better understanding of ritonavir's potential side effects.

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