

# Indirect hyperbilirubinemia and jaundice during chronic hepatitis C in an HIV-infected patient treated with glecaprevir/pibrentasvir (GLE/PIB) and antiretroviral therapy (ART). The first reported case in Italy

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## Keywords

Glecaprevir • Pibrentasvir • HCV • HIV • Chronic hepatitis C • Direct-acting antiviral • Adverse drug reaction

## Summary

*Glecaprevir (GLE)/pibrentasvir (PIB) is a pangenotypic direct-acting antiviral regimen approved for treating chronic hepatitis C virus. Primary treatment and re-treatment with GLE/PIB are effective and safe for patients without decompensated liver cirrhosis and chronic hepatitis C in a real-world clinical setting. However, in the context of compensated cirrhosis and concomitant administration of inhibitors of cytochromes, a careful monitoring of liver biomarkers, as well as therapeutic drug monitoring (TDM), may be advisable during GLE/PIB therapy. The GLE / PIB combina-*

*tion is very effective and safe in achieving a sustained virological response, but it can be associated with the development of severe hepatic adverse events, which require virological and serum concentration monitoring of the two drugs to prevent a serious liver damage. The possible onset of hyperbilirubinemia must not necessarily lead to the suspension of therapy, because the phenomenon may be transient. We report what is likely the first known case of severe jaundice after treatment with GLE/PIB in Italy in a patient with compensated chronic hepatitis in the context of HIV disease.*

## Introduction

Real-world evidence indicates that Glecaprevir (GLE)/pibrentasvir (PIB) 300 mg/120 mg once daily (Mavyret/Maviret), Hepatitis C Virus Direct-Acting Antivirals is a well-tolerated and highly effective for a broad range of HCV-infected patients.

The combination of GLE and PIB, a pan-genotypic and ribavirin-free direct acting antiviral agent regimen, has shown significant efficacy and very few serious complications and was recently approved for chronic hepatitis C virus (HCV) infection

These drugs block two essential enzymes for the replication of HCV. GLE blocks the action of NS3/4A protease, while PIB blocks a NS5A, a key enzyme in HCV RNA polymerization [1]. The most common side effects with GLE/PIB are headache and tiredness. According to EASL guidelines, no dose adjustment of Maviret is required in patients with mild hepatic impairment (Child-Pugh A). GLE/PIB is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C). Presence of cirrhosis, older age, and high body weight were identified as significantly associated with increased GLE/PIB exposure (high body weight is

associated with increased exposure to PIB) [2].

## CASE REPORT

We report the first case of serious indirect hyperbilirubinemia and jaundice observed in Italy in an HIV-infected patient treated with GLE/PIB and antiretroviral therapy (ART). A 55-year-old man with a history of HIV infection in ART (Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg) and compensated liver disease (without cirrhosis), due to chronic hepatitis C virus (HCV) genotypes 4, was admitted to our hospital because of jaundice, tiredness, fatigue, and asthenia. It is well known that no dose adjustment of elvitegravir/cobicistat/ emtricitabine/ tenofovir alafenamide is recommended in patients treated with GLE/PIB.

However, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3 inhibition by cobicistat, and OATP inhibition by elvitegravir may lead to an increase plasma concentration of glecaprevir and pibrentasvir that are P-gp, BCRP, and OATP inhibitors. At 10 weeks following treatment with GLE/PIB, our patient showed evidence of jaundice and severe hyperbilirubinemia (Total bilirubin 12.76 mg/dL, direct bilirubin 7.14 mg/dL). The ALT and AST levels were within the

normal range. At baseline: Cd4+ cells count 374, HIV-RNA < 20 copies/mL, HCV-RNA 1.490.000 UI/mL. Fibrosis stage: F3. Plasma concentrations of GLE/PIB was performed using blood samples taken 1 hour before taking Maviret tablets and 6 and 12 hours after this dose. Plasma samples for determination of GLE and PIB concentrations were analyzed through a UltraHigh Performance Liquid Chromatography coupled with Tandem Mass Spectrometry (UHPLC-MS/MS) method at the Laboratory of Clinical Pharmacology and Pharmacogenetics, University of Turin. Plasma levels of GLE and PIB were as follows: GLE 2472 ng/mL, PIB 92 ng/mL (T0); 8758 ng/mL, PIB 187 ng/mL (T2); GLE8239 ng/mL, PIB 272 ng/mL (T4); GLE 7314, PIB 256 ng/mL (T8), respectively (for GLE higher than the drug concentration in healthy adults). The mean value of glecaprevir maximum plasma concentration level was reported as 1,150 to 1,390 ng/mL in normal healthy adult subjects [3]. Patient was treated with ursodeoxycholic acid, silylline, vitamin E and he received adequate rehydration therapy. He completed GLE/PIB treatment, maintaining an excellent virological response during a close monitoring of liver function. Completed 12 weeks after the end of the treatment, total bilirubin has returned to normal values. Blood examinations were performed at end of treatment (EOT), and at 3, 6, and 12 months post-treatment during the 12-month follow-up period.

## Discussion

GLE/PIB are direct-acting antiviral agents with pangenotypic activity and a high barrier to resistance. GLE/PIB are primarily eliminated via biliary excretion; they are minimally metabolized with < 1% renal excretion and have high percentages of plasma protein binding (98% for glecaprevir and > 99% for pibrentasvir) [4]. The safety of PIB and GLE was evaluated in phase II and III clinical trials. Some caution is needed administering for the co-administration of drugs that are substrates of CYP3A, since GLE is a weak CYP3A inhibitor [5]. In HIV-HCV coinfecting patients, GLE/PIB is contraindicated with atazanavir-containing regimens and is not recommended with other HIV protease inhibitors. Similarly, the inducing non-nucleoside reverse transcriptase inhibitors efavirenz, etravirine and nevirapine are not recommended because of an expected reduction in plasma exposure of glecaprevir/pibrentasvir. All other antiretroviral drugs can be co-administered, including cobicistat when used with integrase inhibitor elvitegravir [5]. However, co-administration of GLE/PIB with medicinal products that inhibit P-gp and BCRP (e.g. ciclosporin, cobicistat, dronedarone, itraconazole, ketoconazole, ritonavir) may slow elimination of GLE/PIB, increasing their plasma levels.

Since cobicistat is an inhibitor of OATP1B3, of P-gp and BCRP, it is expected to increase the systemic exposure to GLE [6].

In a study that evaluated the drug-drug interaction and safety of GLE/PIB coadministration in healthy volunteers,

the combination of GLE/PIB at doses up to 400 mg was well tolerated by the healthy subjects in this study, while high GLE exposures at 700 and 1200 mg were associated with grade 2/3 elevations in alanine aminotransferase, aspartate aminotransferase, and/or bilirubin [7]. Elevations in total bilirubin of at least 2x ULN were observed in 1% of subjects related to glecaprevir-mediated inhibition of bilirubin transporters and metabolism. Bilirubin elevations were asymptomatic, transient, and typically occurred early during treatment. Bilirubin elevations were predominantly indirect, mostly in patients with pre-existing elevated bilirubin levels (consistent with Gilbert's Syndrome), and not associated with ALT elevations [8]. GLE/PIB was safe and efficacious in a dedicated Phase III trial [9] for patients with compensated liver cirrhosis (EXPEDITION-1) who had not elevations in ALT and no patients prematurely discontinued treatment because of adverse events. No cases consistent with a drug-induced liver injury were reported in an integrated analysis from 9 Phase II and III clinical trials, assessing the efficacy and safety of GLE/PIB treatment in patients with compensated liver disease [10]. Grade 3 transient elevations in indirect bilirubin were observed in 1% in patients, particularly in patients who had already grade 1 or 2 elevations before treatment. Most of these elevations were transient in nature and predominantly resulted from increased, indirect bilirubin fractions, which is consistent with the known capability of GLE to inhibit bilirubin transport and conjugation. Higher GLE and/or PIB exposures may be expected in HCV-infected patients with Child-Pugh-B and CP-C hepatic impairment than in HCV-infected subjects with compensated cirrhosis [11]. Co-administration of GLE/PIB with medicinal products that inhibit P-gp and BCRP (e.g. ciclosporin, cobicistat, dronedarone, itraconazole, ketoconazole, ritonavir) may slow elimination of GLE/PIB, increasing their plasma levels. Furthermore, drugs that inhibit OATP1B1/3 (e.g. elvitegravir, ciclosporin, darunavir, lopinavir) increase systemic concentrations of glecaprevir [6]. GLE plasma levels were increased by ritonavir boosted protease inhibitors and cobicistat boosted elvitegravir [12]. Zhang J et al. observed presented reported two patients with hyperbilirubinemia as a side effect and potential for cirrhotic decompensation with renal failure during treatment with GLE/PIB. After GLE/PIB was held bilirubin showed rapid improvement [13]. Yoon JH et al. reported the first known case of severe jaundice after medication with GLE/PIB in a patient with compensated liver cirrhosis, with a plasma drug concentration level of GLE more than 15 times higher than the drug concentration level verified in normal adults [14]. This phenomenon was related to a low activity of CYP3A. In a Taiwanese investigation on the profile of GLE/PIB, 3 (2%) patients had Grade 3 elevation of total bilirubin level [15]. One of them had active HCC and received sorafenib along with radiotherapy before the initiation of GLE/PIB. The patient temporarily discontinued GLE/PIB for 5 days and resumed the scheduled treatment after the recovery of hyperbilirubinemia. The other 2 patients had total bilirubin levels peaked at 4.05 mg/dL and 3.42 mg/

dL, respectively; both completed the assigned treatment without interruption. In the CERTAIN-1 Study, a phase 3, open-label, multicenter study assessing the safety and efficacy of GLE/PIB (300/120 mg) once daily in Japanese patients with chronic HCV GT1 infection, blood bilirubin increased in 3 (2%) patients of Arm A (Patients randomized to 8 weeks of treatment with GLE/PIB), in 3 (6%) patients in the Arm B (Patients randomized to 12 weeks of treatment with ombitasvir/paritaprevir/ritonavir), and in 1 (3%) patient in the Arm C (Patients with compensated cirrhosis assigned to 12 weeks of GLE/PIB, 300/120 mg) [16]. In the CERTAIN-2 Study, assessing the safety and efficacy of GLE/PIB in treatment-naïve patients without cirrhosis, blood bilirubin increased in 1 (1%) patient in arm A (Patients administered GLE/PIB for 8 weeks) and in 7 (15%) patients in the Arm B (Patients administered sofosbuvir + ribavirin for 12 weeks) [17].

For patients (with or without compensated cirrhosis) treated with G/P, no grade  $\geq 3$  abnormalities occurred in hemoglobin, ALT, AST, or total bilirubin levels. Clinically significant laboratory abnormalities occurred in less than 1% of patients and four patients (1 patient was HIV+) had grade 3 elevations in total bilirubin levels. All patients with bilirubin elevations of grade 3 also had bilirubin elevations of grade 1 or 2 at baseline [18].

The Food and Drug Administration (FDA) has received reports that the use of GLE/PIB, elbasvir+grazoprevir (Zepatier), or sofosbuvir + velpatasvir + voxilaprevir (Vosevi) to treat chronic hepatitis C in patients with moderate to severe liver impairment has resulted in rare cases of worsening liver function or liver failure identified in 63 cases (Mavyret, n = 46, Zepatier, n = 14, and Vosevi, n = 3), reported in the FDA Adverse Event Reporting System (FAERS) database and in the medical literature through January 8, 2019 [19]. This occurred most commonly in the first 4 weeks of therapy, most of the patients had Child-Pugh B or C cirrhosis, and liver related events included hyperbilirubinemia (n = 42), jaundice (n = 32), ascites (n = 27), and hepatic encephalopathy (n = 12). Ten cases reported isolated hyperbilirubinemia and jaundice without concomitant evidence of increased transaminase levels or other hepatic decompensation events, and eight cases reported deaths. The median time to onset of a liver-related event or liver decompensation after initiating treatment was 22 days, ranging from 2 days to 16 weeks. The most frequently reported liver related events were hyperbilirubinemia (n = 42), jaundice (n = 32), ascites (n = 27), and hepatic encephalopathy (n = 12). Discontinuation of the drug resulted in resolution of symptoms or reduced liver biochemical values in 39 of the 63 cases, and there were two cases of recurrence of symptoms upon re-initiating treatment [19].

In conclusion, our described case suggests that the concomitant boosting effect of COBI and the reduced elimination of GLE related to cirrhosis can be capable of increase GLE exposure up to potentially toxic levels, causing bilirubin elevation and jaundice. Nevertheless, even in such a particular case, the elevations in bilirubin resulted not associated with liver injury and did not lead

to treatment discontinuation or failure due to toxicity. Therefore, we suggest that, in the context of compensated cirrhosis and concomitant administration of inhibitors of cytochromes, a careful monitoring of liver biomarkers, as well as therapeutic drug monitoring (TDM), may be advisable during GLE / PIB therapy. The possible onset of hyperbilirubinemia must not necessarily lead to the suspension of therapy, because the phenomenon may be transient. In cases of elevation of grade 2-3 of bilirubin, hospitalization for direct, more regular and prudent observation, may be advisable; the administration of liver protective agents and adequate rehydration can favor and improve the adverse event.

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## Conflict of interest

The authors declare no conflict of interest.

## Authors' contributions

All the authors contributed to the study of the clinical case and to the drafting of the manuscript.

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