Systematic analysis of safety profile for darunavir and its boosted agents using data mining in the FDA Adverse Event Reporting System database

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This current investigation was aimed to generate signals for adverse events (AEs) of darunavir-containing agents by data mining using the US Food and Drug Administration Adverse Event Reporting System (FAERS). All AE reports for darunavir, darunavir/ritonavir, or darunavir/cobicistat between July 2006 and December 2019 were identified. The reporting Odds Ratio (ROR), proportional reporting ratio (PRR), and Bayesian confidence propagation neural network (BCPNN) were used to detect the risk signals. A suspicious signal was generated only if the results of the three algorithms were all positive. A total of 10,756 reports were identified commonly observed in hepatobiliary, endocrine, cardiovascular, musculoskeletal, gastrointestinal, metabolic, and nutrition system. 40 suspicious signals were generated, and therein 20 signals were not included in the label. Severe high signals (i.e. progressive extraocular muscle paralysis, acute pancreatitis, exfoliative dermatitis, acquired lipodystrophy and mitochondrial toxicity) were identified. In pregnant women, umbilical cord abnormality, fetal growth restriction, low birth weight, stillbirth, premature rupture of membranes, premature birth and spontaneous abortion showed positive signals. Darunavir and its boosted agents induced AEs in various organs/tissues, and were shown to be possibly associated with multiple adverse pregnant conditions. This study highlighted some novel and severe AEs of darunavir which need to be monitored prospectively.

The burden of morbidity and mortality associated with human immunodeficiency virus (HIV) infection has become a serious public health problem globally1. WHO and most national guidelines recommended all people living with HIV to start antiretroviral therapy (ART) irrespective of clinical or immune status1,2. Earlier initiation of ART has led to an overall improvement in disease control, and the annual number of people dying from HIV-related causes has declined by 60% since the peak in 20043. However, the increasing use of antiretroviral agents has raised potential safety concerns of these drugs which need to be systemically analyzed.

Darunavir, a nonpeptidic inhibitor of the HIV-1 protease with potent activity against resistant virus, was initially approved by the Food and Drug Administration (FDA) in 2006 for the treatment of antiretroviral-experienced adults, and later for naive adults. It must be co-administered with a boosting agent, either ritonavir or cobicistat. In 2008, FDA required labeling change of darunavir, warning the safety issues. In recent years, multiple studies reported the adverse events (AEs) of darunavir-containing agents related to hepatic4 and skin system5. In addition, darunavir was considered a preferred protease inhibitor (PI) for pregnant females living with HIV by the Health and Human Service (HHS) panel, its safety information during pregnancy was still under ongoing monitoring6. In 2015, the antiretroviral pregnancy registry steering committee suggested that prenatal exposure to PIs can lead to increased risk of miscarriage and low birth weight7. Nevertheless, clinical data on pregnancy outcomes and fetal safety after darunavir exposure during pregnancy are limited.

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The primary aim of this pharmacovigilance study was to characterize the safety profile of darunavir-containing agents relating to various organ systems, moreover, evaluate the perinatal outcomes in HIV mothers exposed to darunavir during pregnancy using data-mining of FDA Adverse Event Reporting System (FAERS).

**Results**

**Descriptive analysis.** During the study period, a total of 11,170,959 reports were submitted to FAERS, of which 10,756 reports and 27,234 AEs for darunavir and its boosted agents, making each report contributing 2.53 AEs in average. Table 1 described the characteristics of AE reports submitted for darunavir. Higher rate of male patients (n = 5898, 54.47%) was reported than female patients (n = 3111, 28.92%); 49.31% of the AEs occurred in people aged 18–60 years; serious adverse events (SAEs) accounted for a relatively high proportion (41.47%), with hospitalization and prolonged hospitalization being the most reported outcome (32.57%).

| Gender       | N. of reported AEs | Ratio (%) |
|--------------|--------------------|-----------|
| Male         | 5859               | 54.47     |
| Female       | 3111               | 28.92     |
| Unknown      | 1786               | 16.61     |

| Age group, (y) | N. of reported AEs | Ratio (%) |
|----------------|--------------------|-----------|
| < 18           | 477                | 4.43      |
| 18–44          | 2490               | 23.15     |
| 45–64          | 2814               | 26.16     |
| 65–74          | 342                | 3.18      |
| ≥ 75           | 101                | 0.94      |
| Unknown        | 4532               | 42.13     |

| Reporters      | N. of reported AEs | Ratio (%) |
|----------------|--------------------|-----------|
| Doctors        | 3950               | 36.72     |
| Pharmacists    | 1022               | 9.50      |
| Other medical staff | 3628          | 33.73     |
| Lawyers        | 18                 | 0.17      |
| Consumers      | 1836               | 17.07     |
| Unknown        | 302                | 2.81      |

| SAEs*          | N. of reported AEs | Ratio (%) |
|----------------|--------------------|-----------|
| Death          | 102                | 0.95      |
| Life-threatening| 526               | 4.89      |
| Hospitalization (initial or prolonged) | 3503 | 32.57 |
| Disability     | 329                | 3.06      |

*Serious adverse events.

**Signals of SDR and BCPNN.** When AEs were classified with System Organ Class (SOC) of Medical Dictionary of Regulatory Activities (MedDRA), the positive signals detected by the three algorithms were consistent, involving 11 organ systems: liver, kidney, metabolic and nutritional system, endocrine system, eye, cardiac system, musculoskeletal system, nervous system, skin, gastrointestinal tract, and perinatal periods (Table 2). Disproportionate reporting (SDR) and Bayesian confidence propagation neural network (BCPNN) of the standardized MedDRA queries (SMQs) analysis were summarized in Table 3. 13 SMQs emerged with statistical significance.

Further analyses conducted at the PT level revealed 40 suspicious signals, 20 of which were not included in the label. Among them, 6 suspicious signals were generated in hepatobiliary system, including hepatocyte injury, hyperbilirubinemia, cholestasis, etc.; 6 signals in kidney and urinary system, including renal tubular necrosis, decreased glomerular filtration rate, and proteinuria; 3 in metabolism and nutrition system: hypertriglyceridaemia, hypercholesterolaemia and hypokalaemia; 1 in cardiovascular system: blood creatine phosphokinase increased; 1 in musculoskeletal system: rhabdomyolysis; 4 in skin and subcutaneous tissue: rash generalized, pruritus, dermatitis exfoliative, and Stevens-Johnson Syndrome; 4 in gastrointestinal system: diarrhea, gastrointestinal disorder, oesophageal candidiasis, and acute pancreatitis. It was worth noting that darunavir-containing agents can induce progressive ophthalmoplegia, lipodystrophy acquired, mitochondrial toxicity, adrenal suppression and other severe high strength signals (Table 4).

Among pregnant women, umbilical cord abnormality, foetal growth restriction, low birth weight baby, stillbirth, premature rupture of membrane, premature baby and abortion spontaneous showed positive signals (Table 5). When detected separately, signals of abortion spontaneous and foetal growth restriction for darunavir/cobicistat were positive, and premature baby for darunavir/ritonavir positive (Table 6).
Discussion

As far as we know, this is the first comparative safety study on FAERS that aimed to assess the reported AEs of darunavir and its boosted agents. Overall, three main findings emerged: (1) AEs related to darunavir exposure involve various organs or tissues. We found statistically significant signals in the liver, kidney, metabolic and nutritional system, eye, cardiac system, musculoskeletal system, nervous system, skin, and gastrointestinal tract when classified with SOC, and 13 SMQs involving various systems emerged. (2) Strongly positive signals related to mitochondrial toxicity (ROR = 171.92, PRR = 136.03, $\chi^2 = 9713.13$, IC-2SD = 5.42) and eye disorders (included diplopia, eyelid ptosis, and progressive external ophthalmoplegia) were revealed for the very first time. (3) Signals for adverse pregnancy outcomes were detected in our study, which highlights its safety concern during pregnancy.

Studies indicated that some degree of serum aminotransferase elevations occurred in a high proportion of patients with darunavir. Our study uncovered positive signals for hepatocellular injury and elevation in serum hepatic enzymes which were consistent with the previous findings. Apart from hepatocellular injury, we also found darunavir can induce increased bilirubin, cholestasis, and jaundice which were not observed in clinical studies. Yancheva reported a case of darunavir-related cholestatic hepatitis in an HIV patient in the third year of his antiretroviral therapy. The toxic intermediates may be the cause of some liver injury. It is worth noting that, except for hepatocellular injury, cholestasis should also be monitored when darunavir is prescribed.

### Table 2.

| SOCa | RORb (95%CI) | PRRc ($\chi^2$) | ICd (IC-2SD) |
|------|--------------|----------------|--------------|
| Hepatobiliary disorders | 3.03 (2.88–3.20) | 2.72 (1882.57) | 1.44 (1.41) |
| Renal and urinary disorders | 2.45 (2.33–2.57) | 2.19 (1341.86) | 1.13 (1.10) |
| Metabolism and nutrition disorders | 2.44 (1.35–1.56) | 2.41 (103.75) | 0.50 (0.47) |
| Endocrine disorders | 13.92 (12.43–15.59) | 13.55 (3585.85) | 3.69 (3.65) |
| Eye disorders | 21.44 (18.63–24.66) | 21.05 (3783.56) | 4.24 (4.20) |
| Cardiac disorders | 2.03 (1.01–2.24) | 2.04 (4.05) | 0.04 (0.01) |
| Musculoskeletal and connective tissue disorders | 7.96 (7.33–8.65) | 7.58 (3374.00) | 2.90 (2.87) |
| Nervous system disorders | 7.16 (6.48–7.90) | 6.93 (2061.09) | 2.76 (2.73) |
| Skin and subcutaneous tissue disorders | 10.90 (10.28–11.57) | 9.75 (9877.79) | 3.26 (3.23) |
| Gastrointestinal disorders | 10.10 (9.58–10.65) | 8.71 (11,314.98) | 3.11 (3.08) |
| Pregnancy, puerperium and perinatal conditions | 12.63 (12.05–13.24) | 10.26 (18,528.56) | 3.34 (3.31) |

### Table 3.

| SMQsa | RORb (95%CI) | PRRc ($\chi^2$) | ICd (IC-2SD) |
|------|--------------|----------------|--------------|
| Cholestasis and jaundice of hepatic origin | 4.73 (4.25–6.23) | 4.02 (4524.3) | 1.65 (1.60) |
| Proteinuria | 2.16 (1.56–4.01) | 2.54 (891.2) | 1.19 (1.12) |
| Lipodystrophy | 2.78 (2.50–5.94) | 2.14 (1562.4) | 1.02 (1.01) |
| Hyperglycaemia/new onset diabetes mellitus | 1.41 (1.02–2.31) | 1.36 (2301.5) | 0.92 (0.89) |
| Severe cutaneous adverse reactions | 12.45 (10.87–13.23) | 10.98 (12,541.2) | 3.72 (3.54) |
| Central nervous system vascular disorders | 1.56 (1.11–1.97) | 1.25 (569.7) | 0.51 (0.49) |
| Noninfectious diarrhoea | 6.84 (6.12–7.45) | 6.08 (5423.1) | 2.71 (2.66) |
| Dyslipidaemia | 2.39 (1.52–3.41) | 2.22 (532.3) | 1.24 (1.01) |
| Acute pancreatitis | 4.12 (3.97–4.85) | 4.05 (5213.4) | 2.87 (2.69) |
| Angioedema | 1.29 (1.17–1.56) | 1.21 (2125.6) | 0.56 (0.52) |
| Gastrointestinal nonspecific inflammation and dysfunctional conditions | 3.29 (3.07–4.85) | 3.14 (4524.3) | 1.82 (1.79) |
| Hypersensitivity | 8.56 (7.41–9.52) | 8.41 (9541.2) | 3.02 (2.98) |
| Pregnancy, labour and delivery complications and risk factors | 13.25 (12.89–15.68) | 12.98 (12,679.8) | 3.18 (3.09) |
| PTs\(^a\) | N\(^b\) | ROR\(^c\) (95% CI) | PRR\(^d\) (\(\chi^2\)) | IC\(^e\) (IC-2SD) | Label\(^f\) |
|---|---|---|---|---|---|
| **Hepatobiliary disorders** | | | | | |
| Hepatocellular injury | 105 | 12.00 (9.89–14.56) | 11.89 (1025.76) | 3.42 (3.38) | Yes |
| Liver function test abnormal | 88 | 3.93 (3.18–4.85) | 3.90 (186.81) | 1.91 (1.88) | Yes |
| Hepatic enzyme increased | 147 | 3.80 (2.85–5.05) | 3.78 (90.29) | 1.83 (1.80) | Yes |
| Jaundice | 72 | 3.28 (2.60–4.13) | 3.26 (110.46) | 1.66 (1.62) | No |
| Cholestasis | 78 | 7.61 (6.09–9.52) | 7.57 (435.14) | 2.80 (2.76) | No |
| Hyperbilirubinemia | 46 | 7.62 (5.70–10.19) | 7.60 (255.16) | 2.73 (2.68) | No |
| **Renal and urinary disorders** | | | | | |
| Acute kidney injury | 164 | 2.53 (2.17–2.95) | 2.51 (148.32) | 1.32 (1.28) | Yes |
| Renal impairment | 150 | 3.49 (2.97–4.10) | 3.46 (259.46) | 1.32 (1.29) | Yes |
| Blood creatinine increased | 116 | 2.84 (2.36–3.41) | 2.82 (134.12) | 1.49 (1.44) | Yes |
| Glomerular filtration rate decreased | 35 | 6.86 (4.92–9.57) | 6.84 (167.83) | 2.55 (2.50) | Yes |
| Proteinuria | 53 | 5.44 (4.40–5.57) | 5.75 (202.23) | 2.40 (2.35) | No |
| Renal tubular necrosis | 37 | 6.93 (5.01–9.58) | 6.91 (180.08) | 2.57 (2.53) | No |
| **Metabolism and nutrition disorders** | | | | | |
| Hypertriglyceridaemia | 49 | 15.81 (11.92–20.98) | 15.75 (662.25) | 3.59 (3.53) | Yes |
| Hypercholesterolaemia | 36 | 7.31 (5.26–10.15) | 7.29 (187.79) | 2.63 (2.58) | Yes |
| Hypokalaemia | 40 | 1.57 (1.15–2.15) | 2.57 (7.78) | 0.63 (0.60) | No |
| **Endocrine disorders** | | | | | |
| Hyperglycaemia | 60 | 2.78 (3.16–3.59) | 2.77 (66.29) | 1.43 (1.39) | Yes |
| Adrenal insufficiency | 54 | 11.89 (9.08–15.56) | 11.83 (519.06) | 3.29 (3.24) | No |
| Adrenal suppression | 28 | 44.60 (30.54–65.14) | 44.49 (1100.12) | 4.13 (4.02) | No |
| **Eye disorders** | | | | | |
| Diplopia | 63 | 4.24 (3.31–5.43) | 4.22 (151.11) | 2.00 (1.97) | No |
| Eyelid ptosis | 59 | 10.43 (8.06–13.49) | 10.38 (486.02) | 3.15 (3.11) | No |
| Progressive external ophthalmoplegia | 49 | 1761.17 (1112.25–2788.69) | 1753.15 (31,253.87) | 3.54 (3.21) | No |
| **Cardiac and vascular disorders** | | | | | |
| Blood creatine phosphokinase increased | 73 | 3.47 (2.76–4.37) | 3.46 (124.84) | 1.74 (1.70) | Yes |
| **Musculoskeletal and connective tissue disorders** | | | | | |
| Rhabdomyolysis | 76 | 3.00 (2.39–3.76) | 2.99 (98.36) | 1.54 (1.51) | YeS |
| **Nervous system disorders** | | | | | |
| Nervous system disorder | 45 | 1.76 (1.31–2.36) | 3.68 (235.32) | 0.79 (0.76) | No |
| Neuropathy peripheral | 119 | 2.50 (2.08–3.00) | 2.48 (103.91) | 1.29 (1.26) | No |
| **Skin and subcutaneous tissue disorders** | | | | | |
| Rash generalised | 74 | 2.34 (1.87–2.95) | 2.34 (55.32) | 1.20 (1.17) | Yes |
| Pruritus | 44 | 2.55 (1.15–2.09) | 2.32 (54.21) | 0.61 (0.58) | Yes |
| Dermatitis exfoliative | 53 | 10.26 (7.83–13.46) | 10.22 (46.74) | 3.11 (3.07) | Yes |
| Stevens-Johnson Syndrome | 47 | 3.11 (2.33–4.14) | 3.10 (64.68) | 1.57 (1.53) | Yes |
| **Gastrointestinal disorders** | | | | | |
| Diarrhoea | 405 | 1.21 (1.12–1.37) | 2.23 (18.11) | 0.30 (0.27) | Yes |
| Gastrointestinal disorder | 84 | 1.71 (1.38–2.12) | 2.71 (24.03) | 0.76 (0.73) | Yes |
| Oesophageal candidiasis | 37 | 16.02 (11.57–22.18) | 15.97 (496.77) | 3.50 (3.44) | No |
| Pancreatitis acute | 59 | 4.21 (3.26–8.44) | 4.19 (139.96) | 1.26 (1.23) | Yes |
| **Others** | | | | | |
| Virologic failure | 254 | 117.48 (103.06–133.93) | 114.73 (256.88) | 6.02 (6.14) | No |
| Drug resistance | 224 | 17.31 (15.15–19.78) | 16.97 (3301.72) | 3.97 (3.93) | No |
| Lipodystrophy acquired | 153 | 137.98 (116.46–163.48) | 136.03 (18133.28) | 6.08 (6.00) | No |
| Viral mutation identified | 75 | 52.98 (41.98–66.86) | 52.62 (5565.80) | 4.93 (4.85) | No |
| Mitochondrial toxicity | 68 | 171.92 (132.93–222.34) | 107.84 (9713.13) | 5.56 (5.42) | No |
| Angioedema | 42 | 1.47 (1.09–1.99) | 2.47 (15.84) | 0.54 (0.51) | Yes |
| Erectile dysfunction | 29 | 2.03 (1.41–2.93) | 2.03 (14.19) | 0.97 (0.94) | No |

Table 4. Signal strength for darunavir and its boosted agents based on PT level in FAERS. *PT: preferred terms. †Number of patients with adverse events. ‡ROR reporting odds ratio. The lower limits of the 95% CI of the ROR greater than 1 indicated statistically significant RORs. §PRR proportional reporting ratio. PRR and \(\chi^2\) greater than 2 and 4 respectively indicated statistically significant PRRs. ¶Information component. The signal was statistically significant when IC-2SD > 0. ¶¶Whether adverse events are mentioned in the drug label or not.
In our study, 6 positive signals of the renal and urinary system were detected (AKI, renal impairment, blood creatinine increased, glomerular filtration rate decreased, proteinuria, and renal tubular necrosis). It was showed that cobicistat inhibits tubular secretion of creatinine without affecting actual glomerular function. This should be considered when interpreting changes in creatinine. Besides, our study uncovered an association of darunavir with nephrolithiasis, which might be one of the causes of kidney injury. On the other hand, we should take caution explaining the significant signal of darunavir in renal injury, since HIV-associated nephropathy is one of the complications in advanced HIV disease, the main manifestations of which were heavy proteinuria and a decline in kidney function. In accord with this assumption, drug resistance and treatment failure are significantly noted in the analysis, which implicated the occurrence of advanced HIV disease.

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Table 5. Signal strength of pregnancy, puerperium and perinatal conditions for darunavir and its boosted agents. aPT: Preferred terms. bNumber of patients with adverse events. cROR reporting odds ratio. The lower limits of the 95% CI of the ROR greater than 1 indicated statistically significant RORs. dPRR proportional reporting ratio. PRR and \( \chi^2 \) greater than 2 and 4 respectively indicated statistically significant PRRs. eInformation component. The signal was statistically significant when IC-2SD > 0.

| PT† | Darunavir/cobicistat | Darunavir/ritonavir |
|-----|----------------------|---------------------|
|     | N | ROR (95%CI) | ROR (\( \chi^2 \)) | IC (IC-2SD) | N | ROR (95%CI) | PRR (X2) | IC (IC-2SD) |
| Foetal exposure during pregnancy | 813 | 20.73 (19.28–22.28) | 19.24 (13,836.29) | 4.21 (4.18) | 204 | 1.30 (1.14–1.50) | 1.30 (14.12) | 2.33 (2.30) |
| Premature baby | 272 | 16.50 (14.62–18.63) | 16.11 (3789.36) | 3.91 (3.88) | 123 | 0.18 (0.28) | 0.18 (0.28) | 0.18 (0.28) |
| Abortion spontaneous | 269 | 10.87 (9.63–12.28) | 10.62 (2317.55) | 3.35 (3.31) | 80 | 0.86 (0.69–1.07) | 0.86 (1.71) | 0.97 (0.94) |
| Foetal growth restriction | 105 | 37.37 (30.73–45.45) | 37.02 (3519.26) | 4.75 (4.69) | 16 | 1.50 (0.92–2.45) | 1.50 (2.17) | 0.22 (0.19) |
| Low birth weight baby | 95 | 26.54 (21.13–32.56) | 26.31 (2232.29) | 4.35 (4.30) | 5 | 4.42 (4.30) | 4.42 (4.30) | 4.42 (4.30) |
| Stillbirth | 70 | 22.59 (17.81–28.65) | 22.45 (1388.80) | 4.09 (4.03) | 9 | 0.78 (0.40–1.49) | 0.78 (0.38) | 0.33 (0.28) |
| Premature rupture of membranes | 38 | 17.20 (12.48–23.71) | 17.14 (552.58) | 3.58 (3.52) | 9 | 0.78 (0.40–1.49) | 0.78 (0.38) | 0.33 (0.28) |
| Umbilical cord abnormality | 29 | 71.32 (48.94–103.95) | 71.13 (1811.59) | 4.38 (4.25) | 2 | 2.33 (2.30) | 2.33 (2.30) | 2.33 (2.30) |

Table 6. Signal strength of pregnancy, puerperium and perinatal conditions for darunavir/cobicistat and darunavir/ritonavir. aPT: preferred terms. bNumber of patients with adverse events. cROR reporting odds ratio. The lower limits of the 95% CI of the ROR greater than 1 indicated statistically significant RORs. dPRR proportional reporting ratio. PRR and \( \chi^2 \) greater than 2 and 4 respectively indicated statistically significant PRRs. eInformation component. The signal was statistically significant when IC-2SD > 0. *Statistically significant.
down-regulation of the glucose transporter-4, the major transporter of glucose into fat cells, and cardiac and skeletal muscle. Since HIV-positive persons are at increased risk for premature cardiovascular disease (CVD), dyslipidemia and hyperglycemia caused by darunavir can adversely affect the risk factors for CVD. However, the association between darunavir or atazanavir and increased risk of myocardial infarction or stroke has not been established which was seen with other PIs.

Hypokalemia is common in AIDS inpatients, usually due to AIDS-related gastrointestinal complications. Hypokalemia directly caused by darunavir has not been reported, but it was suggested that diarrhea and vomiting were the most common adverse reactions of darunavir, which we presumed might be the cause of hypokalemia.

Adrenal suppression and dysfunction were found related to the use of darunavir-containing agents. The possible explanation may be due to drug-drug interaction of pharmacokinetic boosters with exogenous glucocorticoids. Glucocorticoids, including non-systemic preparations, were widely used in HIV patients for non-AIDS-related conditions. Iatrogenic Cushing’s syndrome can result from the co-administration of ritonavir or cobicistat and synthetic glucocorticoids given by any route. The effects of these boosters on cytochrome P450 lead to prolongation of the half-life of the latter. The resultant high plasma levels of glucocorticoid cause a significantly high strength (ROR = 1761.17, PRR = 1753.15, IC = 3.54). PEO is a myopathic alteration of slow skeletal muscle. It is not surprising to find that, increased creatine phosphokinase and rhabdomyolysis are both positive signals. Mitochondrial toxicity might be a possible explanation for the cause of these AEs.

Other novel AEs inferred to be associated with mitochondrial toxicity were eye disorders, which included diplopia, eyelid ptosis, and progressive external ophthalmoplegia (PEO). Among them, the signal of PEO showed a significantly high strength (ROR = 1761.17, PRR = 1753.15, IC = 3.54). PEO is a myopathic alteration of slow progression which affects extrinsic ocular muscles; ptosis of the eyelid being the most characteristic sign. Some cases progress to eye immobilization. PEO is one of the clinical phenotypes of mitochondrial myopathies. We speculated that darunavir induced eye disorders through mitochondrial toxicity, although the relationship has to be confirmed with rigorous studies.

There is little doubt that mitochondrial toxicity is the major cause of NRTIs-induced myopathy and neuropathy, and we can’t help but speculate the newly found AEs with nervous system disorders (neuropathy and peripheral neuropathy) of darunavir in our study might also be related to mitochondrial toxicity. However, this speculation needs to be further investigated.

We found generalized rash, pruritus, exfoliative dermatitis and Stevens-Johnson Syndrome (SJS) were positive signals in the skin and subcutaneous tissue. In clinical trials, rash occurred in 16% of subjects, which were generally mild-to-moderate. Severe skin rash, including erythema multiforme and SJS has also been reported. The discontinuation rate due to rash was 0.3%. The incidence of SJS is 100-fold higher among HIV individuals. The reasons for the susceptibility are not fully understood, although exposure to multiple medications may contribute. Our study brought to the forefront again the risk of severe adverse skin reactions caused by darunavir.

Our study identified diarrhea, gastrointestinal disorder, esophageal candidiasis, and acute pancreatitis as positive signals in the gastrointestinal system. Diarrhea is one of the most commonly reported adverse reactions for darunavir (10%). Esophageal candidiasis, which is typically seen in patients with HIV who have advanced immunosuppression, may not be directly related to the administration of darunavir, but rather to the failure of antiviral therapy. Acute pancreatitis induced by darunavir-based ARTs has been reported previously. Hypertriglyceridemia and hypercholesteremia related to darunavir may play a role. Besides, it was suggested that mitochondrial toxicity may be the cause of NRTI-induced pancreatitis, the possibility cannot be ruled out that acute pancreatitis is one of the manifestations of darunavir-induced mitochondrial toxicity.

PIs have been a key component of HIV therapy in pregnant women. In 2016, darunavir/ritonavir replaced lopinavir/ritonavir as a recommended agent due to its potent antiretroviral activity and a lower rate of causing lipid abnormality. The fetal transfer rate of darunavir was 12–16%, and a mean concentration of 132 ± 32 ng/mL was identified in the fetal compartment. Such exposure may provide the benefit of pre-exposure prophylaxis, but it could also lead to toxicity. Although teratogenicity has not been identified in animal studies, no well-designed controlled trials have been performed in humans. The antiviral pregnancy registry reported that the risk of birth defects did not increase following darunavir exposure, and darunavir could even play a protective role in the development of microcephaly. Our study showed positive signals for darunavir in terms of premature baby, spontaneous abortion, foetal growth restriction, low birth weight baby, stillbirth, premature rupture of membranes, and umbilical cord abnormality. In the previous studies, preterm birth and low birth weight were the most commonly reported adverse events after pregnancy exposure to PIs. One study suggested that prematurity was independently associated with ritonavir-boosted PI therapy during pregnancy. We further detected signals for darunavir/ritonavir and darunavir/cobicistat respectively, identifying positive signal for darunavir/ritonavir only in prematurity, and darunavir/cobicistat in abortion spontaneous and foetal growth restriction. The result further verified that preterm birth may be more associated with ritonavir. Since the combination of darunavir/cobicistat is not currently recommended during pregnancy due to a lack of safety data for cobicistat, the difference of these two combinations for the offspring need to be further studied.

Despite some steps were taken to make the results more reliable, the following limitations of our study need to be noticed: (1) we derived ROR, PRR, and IC values based on the reported frequency of drug-event combinations, and were adjusted based on the rates reported by other drugs and the rates of all other AEs reported for...
the studied drug. The value indicated an increased risk of AE reporting and not a risk of AE occurrence. (2) The FAERS database is subject to various biases such as under-reporting, over-reporting, duplicates, unverified source of submitted data, missing information, misspelling, etc. (3) Certainty that the drug is in fact responsible for the reported event is absent. This is particularly true for antiretroviral agents since HIV infection per se can induce a higher risk of multi-system complications and are generally treated with a combination of antiviral drugs. The absence of previous exposure to other HIV treatments as well as the stage of disease progression makes it difficult to evaluate the influence of other antiviral drugs and the disease. (4) Except for pregnancy and perinatal conditions, the signal mining was not carried out separately for darunavir, darunavir/ritonavir, and darunavir/cobicistat, making it impossible to distinguish AEs resulted from darunavir and boosters.

Conclusions

The safety profile of darunavir containing agents was reviewed using the AEs submitted to the FAERS. Base on the 10,756 reports, AEs with darunavir and its boosted agents took place in many organs/tissues. An association related to mitochondrial toxicity was identified and was presumed to be associated with the occurrence of AEs in multiple systems (eye, muscle, nerve, etc.). Darunavir was shown to be possibly associated with multiple adverse pregnancy conditions. The usefulness of pharmacovigilance research should be corroborated with the real-world FAERS data; however, further clinical trials and real-world study are required to confirm our findings.

Methods

Data sources. The data for this study were retrieved from the public release of the FAERS database, which adheres to the international safety reporting guidance issued by the International Conference on Harmonisation (ICH E2B). AEs are coded using preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MDRA) terminology. Currently, FAERS comprises more than 12 million reports gathered worldwide. These post-marketing reports contain relevant anonymised information relating to the AEs, include: (1) Demographic and administrative information and the initial report image ID number; (2) Drug information from the case reports; (3) Reaction information from the reports; (4) Patient outcome information from the reports, etc. We conducted a retrospective pharmacovigilance study using data from the FAERS database covering the period from July 2006 to December 2019 through the OpenVigil FDA platform. To ensure data integrity, AE reports for “darunavir”, “darunavir/ritonavir” or “darunavir/cobicistat” were analyzed. The reports were included only if the drug was primary and secondary suspected. We removed duplicated records according to the FDA’s recommendations by selecting the latest FDA_DT when the CASE_ID and FDA_DT were the same, and excluded reports with more than three differences. We also excluded reports with more than 3 items of missing information.

Definition of AEs. SDR and BCPNN were performed using all existent narrow SMQs and SOCs. Further analysis on PT levels was conducted using the same method. Two researchers classified the AEs reports in terms of SMQs, SOCs and PTs, and collected clinical characteristics of the patient, including gender, age, AE outcome, and type of reporter, respectively. Death, life-threatening adverse drug experience, inpatient/prolonged hospitalization, and significant disability/incapacity were defined as SAEs.

Data mining algorithm and statistical analysis. Descriptive analyses were conducted to summarize the clinical characteristics of the patients with darunavir-associated AEs collected from the FAERS database. In this study, the signals of SDR and BCPNN were generated by calculating the reporting odds ratio (ROR), proportional reporting ratio (PRR), information component(IC). These methods were based on two-by-two contingency (Table 7). An association between drug and an AE was identified when all the three algorithms were positive. The equations and criteria for the algorithms are shown in Table 850–52. The analyses were conducted using the Microsoft EXCEL 2010 and SPSS 13.0 statistical software.
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Author contributions
All the authors were involved in the study. X.T., Y.Y. and L.C.: concept and design, acquisition of data, analysis and interpretation of data, manuscript preparation; K.W. and Y.J.: analysis and interpretation of data; G.H.: revision of the manuscript.

Competing interests
The authors declare no competing interests.

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