Table 251.13. Summary of adverse reactions associated with the dolutegravir based on clinical trial experience.

System organ class	Frequency[a]	Preferred term
Immune system disorders	≥ 0.1% and < 1%	Hypersensitivity
	≥ 0.1% and < 1%	Immune reconstitution syndrome
Psychiatric disorders	≥ 1% and < 10%	Insomnia
	≥ 1% and < 10%	Abnormal dreams
	≥ 1% and < 10%	Depression
	≥ 0.1% and < 1%	Suicidal ideation or suicide attempt (particularly in patients with a preexisting history of depression or psychiatric illness)
Nervous system disorders	≥ 10%	Headache
	≥ 1% and < 10%	Dizziness
Gastrointestinal disorders	≥ 10%	Nausea
	≥ 10%	Diarrhea
	≥ 1% and < 10%	Vomiting
	≥ 1% and < 10%	Flatulence
	≥ 1% and < 10%	Upper abdominal pain
	≥ 1% and < 10%	Abdominal pain
	≥ 1% and < 10%	Abdominal discomfort
Hepatobiliary disorders	≥ 0.1% and < 1%	Hepatitis
Skin and subcutaneous tissue disorders	≥ 1% and < 10%	Rash
	≥ 1% and < 10%	Pruritus
General disorders and administration site conditions	≥ 1% and < 10%	Fatigue
Investigations	≥ 1% and < 10%	Creatine phosphokinase elevations[b]

[a]Proportion of dolutegravir program participants reporting event. Associated frequency terminology is as follows: very common (≥ 1/10 program participants reported this), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1,000 and < 1/100), rare (≥ 1/10,000 and < 1/1,000), and very rare (< 1/10,000), including isolated reports.

[b]These were asymptomatic and mainly in association with exercise.

Source: ViiV (data on file).

who used abacavir in their regimen were required by protocol to have screened negative for HLA-B*5701.

In the latest integrated analyses performed for the dolutegravir, there were 17 adult subjects with AE preferred terms of either drug hypersensitivity or hypersensitivity or who had a syndrome indicative of drug hypersensitivity in 1856 subjects (0.91%) exposed to at least one dose of dolutegravir in ViiV-sponsored phase IIb to IIIb clinical trials with completed planned clinical study report analyses. A contribution of dolutegravir to the events could not be ruled out in 5 cases (0.27%), but all of these were potentially confounded by concurrent abacavir, etravirine, and/or darunavir use for which HSR and rash are expected.

Thus the frequency of HSR with dolutegravir in clinical trials remains low, and SAE reports are generally confounded by concurrent antiretroviral therapy. However, given the occurrence of hypersensitivity in dolutegravir recipients, hypersensitivity is an uncommon but recognized risk for ART-containing dolutegravir, regardless of dose.

RASH

The overall reporting rate for rash with dolutegravir in the latest ISO was 5% (91/1843), and was similar for dolutegravir once daily (5%) and dolutegravir twice daily (6%). In INSTI-naive subjects (both ART-naive and -experienced), the rates for dolutegravir were similar to raltegravir and favorable compared with efavirenz, the fixed-dose combination of efavirenz–tenofovir disoproxil fumarate–emtricitabine, and darunavir–ritonavir. Episodes in subjects receiving dolutegravir-containing ART were generally considered of mild to moderate intensity, occurred within the first 10 weeks of treatment, rarely required interruptions or discontinuations of therapy, and tended to resolve within 2–3 weeks. No episodes of serious rash such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme have been reported for the dolutegravir development program to date.

HEPATOBILIARY DISORDERS

Nonclinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with dolutegravir. Due to comorbidities (e.g. hepatitis B [HBV] and HCV co-infection) and co-administered medications in HIV-infected patients, it is recommended to monitor liver chemistries in the clinical setting. For ART-naive subjects, the incidence of grade 3/4 liver chemistry toxicities was low and similar (< 2%) for all liver chemistries in all treatment groups of the phase III/IIIb studies (SPRING-2, SINGLE, and FLAMINGO). The percentage of subjects with ALT over three times the upper limit of normal (ULN) varied between 2% and 5% across all treatment groups of the three phase III/IIIb studies.