Background
Resistance to integrase inhibitors is becoming a critical issue in clinical practice. Among 3012 patients undergoing integrase GRT for clinical decision making 471 patients had viruses with ≥1 raltegravir or elvitegravir resistance mutation (15.6%). In 2015 prevalence of integrase drug resistance mutations was in 6.8/1000 ART-treated patients in British Columbia. DTG 50 mg twice daily has been proven to be effective as rescue therapy in treatment-experienced patients with INI resistance. In VIRKING-3, 60% of subjects achieved >50 (mL in week at 24 4%, 47% and 57% of subjects had HIV-1 RNA >50 and >400 copies/mL at week 24, 48% and 53% at week 48, respectively. No data are available on long-term efficacy of Dolutegravir (DTG, 50 mg twice daily) as rescue therapy in treatment-experienced patients (pts) infected with HIV with persistence of resistance mutations to raltegravir or elvitegravir. Here we evaluated long-term efficacy of DTG 50 mg twice daily in combination with optimized background therapy (OBT) using data from clinical practice.

Methods
The Italian Medicines Agency (AIFA, Agenzia Italiana del Farmaco) requested VIV Healthcare to prospectively collect, since November 2014, demographic, clinical, virological, immunological data of pts treated with DTG 50 mg BID from all the Italian Infectious Diseases Centers in order to monitor the appropriateness of DTG 50 mg BID prescriptions (www.progetto-viva). Highly treatment-experienced failing patients, with integrase inhibitor resistant virus, who started DTG 50 mg twice daily (BID) plus OBT, with ≥1 viral load (VL) during follow-up were included in the analyses. VL and CD4+ values, measured in subjects who started DTG 50mg BID+OBT before November 2014, were retrospectively collected. Patients’ follow-up accrued from the start of DTG 50mg BID+OBT (Baseline) until virological failure or DTG discontinuation or last visit, whichever occurred first.

Virological failure (VF) was defined by: 0) the lack of achievement of undetectable VL (HIV-RNA<50 copies/mL) by 6 months and thereafter; or ii) the occurrence of two consecutive VL >250 copies/mL during follow-up after achievement of undetectable VL. Treatment failure (TF) was defined by the occurrence of VF or discontinuation during follow-up. Genotypic drug-resistance tests were also collected; integrase inhibitors (INI) resistance mutations were classified according to the Stanford HIVdb algorithm.

Results
Overall, 195 HIV-1 infected failing pts, 72% males, age 51 (45-54) years, 91% Italian, HIV infection since 21 (15-25) years, 32C% positive, baseline (BL) VL 365 (42.7-46.4) logc/mL, BL CD4+ 299 (138-538) cells/µL (Table 1). The characteristics of baseline HIV-1 co-receptor tropism and genotypic drug-resistance data are also described in Table 1. During a median follow-up of 17.5 (9.7-33.8) months, 62 TF and 48 VF events occurred (Figure 1); 7 (14%) pts discontinued DTG (10 VF, 9 clinical reasons, 4 deaths due to disease progression, 2 patient’s decision, 1 lost to follow-up, 1 adverse event).

Kaplan Meier curves of TF and VF according to baseline CD4+ (>200, >200 cells/µL) or baseline VL (≤100 000, >100 000 copies/mL) and according to the Q248N/R wild-type mutation at baseline are shown in Figure 2, and Figure 3, respectively.

CD4+ changes since baseline were ±5 (8/118), ±30 (21/258), ±208 (108/310), ±279 (119/399), ±279 (114/427) cells/µL at 12, 24, 36, 48 and 60 months since DTG start, respectively.

BL and follow-up genotypic drug-resistance tests were available in 12 subjects with MT, patient’s characteristics and INI resistance mutations are detailed in Table 2.