Extensive cross-resistance to new and existing integrase inhibitors conferred by accumulation of multiple mutations in vivo

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Background

Integrase inhibitors are the latest class of antiretrovirals for the treatment of HIV to reach clinical practice. Bictegravir (BIC) and cabotegravir (CAB) are the newest integrase inhibitors currently in clinical trials.

The combination of Q148 substitutions and additional substitutions are found commonly in patients failing raltegravir (RAL), elivitegravir (EVG) and dolutegravir (DTG). The combination of G140S/Q148H has been shown to decrease susceptibility to BIC and CAB.[1] However, descriptions of clinically relevant resistance to the newest HIV integrase inhibitors are still relatively limited.

We compared the in vitro phenotypic susceptibility from a panel of twelve patient-derived isolates with these mutations to all five available HIV integrase inhibitors.

Methods

Patient samples collected and extract by the BC Centre for Excellence in HIV/AIDS which contained Q148H and G140S were identified.

Recombinant viruses were constructed and phenotyped as shown by the workflow in Figure 1. Briefly, clonal PCR amplicons were produced by diluting RNA extracts to 500copies/mL, made into recombinant viruses and titered in the MT4-LTR-EGFP cell line using a Spectramax i3 Minimax 300 Imaging cytometer (Molecular Devices). Titred recombinant viruses were phenotyped with 8 concentrations of RAL, EVG, DTG, BIC and CAB ranging from 0nm to 1000nm.

The 50% effective concentrations (EC50s) and fold-changes (FC) in EC50 relative to a NL4.3 control were calculated using in-house scripts. Graphs were made in R.

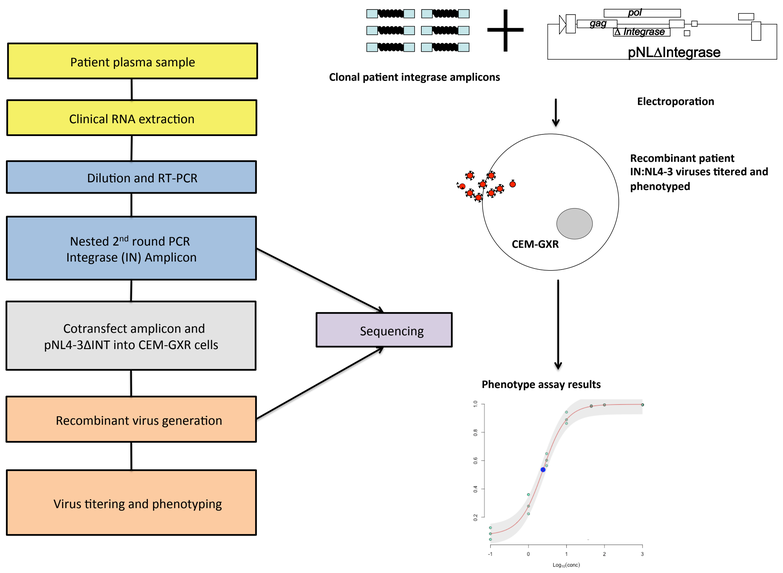

Figure 1.
Recombinant virus construction workflow.

Results

The combination of G140S and Q148H substitutions with additional substitutions, as well as alone, conferred >100 FC in resistance for RAL and EVG. However, G140S and Q148H alone conferred relatively low changes in FC to DTG, BIC or CAB (2-4-fold) (Table 1). Viruses with G140S/Q148H and additional substitutions showed increasing resistance to DTG, BIC and CAB with each additional substitution.

There is extensive cross-resistance between DTG, BIC and CAB, as shown by the strongly correlated phenotypic resistance values (r = 0.97-0.98) (Figure 2).

Table 1. Median (IQR) Fold Change in the 50% effective concentrations (EC50) of recombinant viruses with G140S and Q148H mutations and additional mutations for raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG), bictegravir (BIC) and cabotegravir (CAB).

Mutations	G140S + Q148H	G140S + Q148H + T97A	G140S + Q148H + T97A + L74M
N (patients)	6	2	3
n (viruses)	7	2	3
RAL	>100(>50->100)	>50(>50->50)	>50(>50->50)
EVG	>100(>100->100)	>100(>100->100)	>100(>100->100)
DTG	3.3(2.7-6.1)	25(18-39)	344(283-376)
BIC	2.7(2.1-3.1)	6.6(5.7-9.7)	67(64-72)
CAB	3.7(3.2-4.5)	54(35-92)	448(295-795)

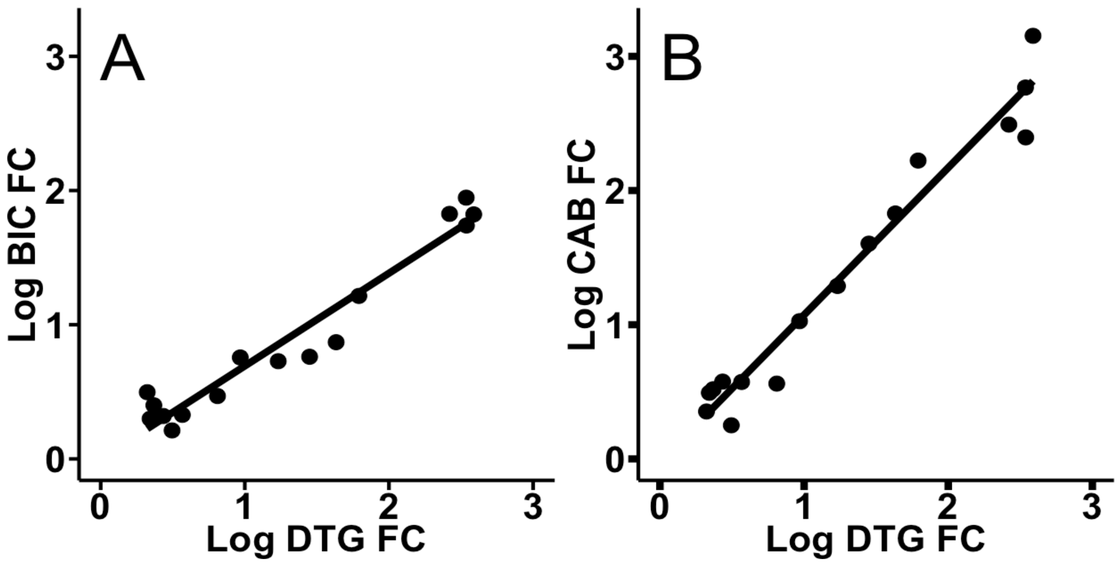

Figure 2.
Correlation between log bictegravir (BIC), cabotegravir (CAB) and Dolutegravir (DTG) fold-change (FC) values for the same sample. A) Log BIC FC versus Log DTG FC. Correlation (r-value) was 0.97 and slope was 0.69. B) Log CAB FC versus Log DTG FC. Correlation (r-value) was 0.98 and slope was 1.1.

Discussion

DTG, BIC and CAB susceptibility was not greatly impacted by G140S/Q148H, however, small shifts in FC may have clinical implications, as seen in the VIKING studies.[2] The accumulation of multiple substitutions in HIV integrase confers high level phenotypic resistance to all available HIV integrase inhibitors in patient-derived samples. Furthermore, there is extensive cross-resistance between DTG, BIC and CAB where phenotypic resistance values were almost colinear.

References

1. Anstett K, Brenner B, Mesplede T, Wainberg MA. HIV drug resistance against strand transfer integrase inhibitors. *Retrovirology* 2017;14(1):36.
2. Castagna A, Maggiolo F, Penco G, et al. . Dolutegravir in Antiretroviral-Experienced Patients With Raltegravir- and/or Elvitegravir-Resistant HIV-1: 24-Week Results of the Phase III VIKING-3 Study. *The Journal of Infectious Diseases* 2014;210(3): 354-362.

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