KEY POINTS

- Viral resistance to bNAbs may compromise their effectiveness at maintain HIV virological suppression, and therefore reliable assays are needed to screen for resistance.
- Sensitivity to the bNAb 10-1074 is associated with specific residues in the HIV Env protein, but more data are needed to confirm the residues associated with resistance to the bNAb 3BNC117.
- Several approaches have been developed to predict bNAb sensitivity, but none are yet adequately reliable for routine use, and larger datasets are needed to improve their accuracy.

and 10-1074, aiming to understand how bNAb resistance emerges, what its effect on viral fitness and functionality might be, and how best to measure it.

10-1074 AND 3BNC117 IN THE CLINIC: ESCAPE SIGNALS

Passive administration of 10-1074 and 3BNC117 – generally intravenously - alone or in combination is being tested as an HIV treatment in an increasing number of clinical trials, [11–13,15,17,18▪▪] with hope for long-term drug-free remission, and even cure. Single infusions of 10-1074 or 3BNC117 in viraemic participants have been shown to transiently reduce viremia in two clinical trials; [10,12] however, sustained or full viral suppression was not achieved. BNAb resistant clones were selected for in all participants that received 10-1074 monotherapy and in the majority of those who received 3BNC117. In an antiretroviral treatment interruption (ATI) setting - with participants who were screened for bNAb sensitivity -infusions of 3BNC117 resulted in longer periods of undetectable viraemia compared to historical controls (average of 6.7 and 9.9 weeks of viral suppression off ART depending on the number of doses, vs. 2.9 weeks in controls) [15]. Moreover, a few participants did not rebound as long as bNAb levels remained therapeutic, which suggests that adequate serum levels of 3BNC117 may prevent the development or selection of escape mutations [15]. However, a 2018 study [14] showed that when 3BNC117 was administered in PWH who underwent ATI, preexisting resistance was a strong predictor of shorter time to viral rebound [14].

As has been learned from the field of antiretroviral therapy, one approach to overcoming resistance is to give drugs together in combination. The joint administration of 10-1074 and 3BNC117followed by ART interruption in PWH with bNAb sensitive viruses mediated viral suppression for an extended period (median 21 weeks) [13] – a longer period than monotherapy – and supporting the argument for combination therapy. These findings were confirmed in the most recent phase 1b clinical trial of 10-1074 and 3BNC117 combination given to PWH on or off antiretroviral treatment [18▪▪]. Of note, when administered to viraemic participants, the combination of 3BNC117 and 10-1074 was not as effective; although a reduction in viremia was observed, full viral suppression was only seen in one participant with a low baseline viral load [11]. This suggests that for bNAbs to be fully effective, viral suppression may first need to be achieved with ART. Only participants with chronic infection were recruited in the clinical trials mentioned above, and it is that treatment in primary infection is more effective due to smaller HIV reservoirs and lower viral diversity.

The longer the duration for which bNAbs are above therapeutic levels, the greater the resulting period of viraemic control. Figure 1 shows summary data from currently published clinical trials and shows that increasing numbers of doses of 3BNC117 alone or combined with 10-1074, result in longer periods of control in participants who interrupted ART immediately after receiving bNAbs (Fig. 1A, B). Cox regression analysis using combined data from studies that report both baseline sensitivity and time to viral rebound [13,18▪▪,19▪▪]showed a 37% decrease in viral rebound per increase in number of bNAb doses (hazard ratio, HR: 0.63, 95% confidence interval, CI: 0.50-0.78, p-value = 0.00004). Also, presence of resistance at baseline was associated with a 44% increase in expected viral rebound relative to absence of resistance (HR: 1.44, 95% CI: 0.60-3.45, p-value = 0.4), although this effect was not statistically significant.(The times to viral rebound for Sneller *et al.* [19▪▪] are sampled by approximation from the paper figures.) One would expect, however, that these data will be strengthened by the results of clinical trials using long-acting 'LS' bNAb variants, which may result in 4-6 months suppression after single dosing.

BROADLY NEUTRALISING ANTIBODIES TARGETING EPITOPES AND ESCAPE MUTATIONS

Common features of bNAbs include extensive somatic hypermutation, the ability to recognise N-glycans as epitopes and long heavy chain complementary determining regions (CDRs) that reach protein epitopes concealed by the glycan shield or other Env protein loops. BNAbs target conserved HIV Env sites, which include the CD4 binding site (CD4bs), the V3 glycan site, the V2 apex, the MPER