PROLONGED VIRAL SUPPRESSION BY IMMUNOTHERAPY WITH ANTI-HIV ANTIBODIES 3BNC117 AND 10-1074

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Background:

Broad and potent monoclonal anti-HIV-1 antibodies (bNabs) comprise a promising class of immunotherapeutics that have the potential to suppress HIV-1 infection, increase the rate of infected cell clearance and enhance anti-HIV immunity. However, bNabs have only been tested in short term studies and their effects on the intact latent reservoir have not been interrogated in depth. Here we report on a clinical study in which people living with HIV who started ART during chronic infection received 7 doses of a combination of two bNabs over a period of 20 weeks in the presence or absence of antiretroviral therapy (ART).

Methods:

We conducted a phase 1b, open label, randomized clinical trial of the combination of two bNabs, 3BNC117 and 10-1074, in the presence or absence of ART, including two study groups of people living with HIV-1 on suppressive ART for at least 12 months prior to entry (NCT03526848). Study participants were enrolled without prior screening for proviral reservoir sensitivity to 3BNC117 or 10-1074. Participants in Group 1 discontinued ART 2 days after the first 3BNC117 and 10-1074 infusions, while participants in Group 2 remained on ART during the period of antibody infusions through week 26 (**Fig. 1**). Participants in both groups received up to seven infusions of 30 mg/kg of each antibody over the course of 20 weeks and were followed for a total of 48 weeks from enrollment.

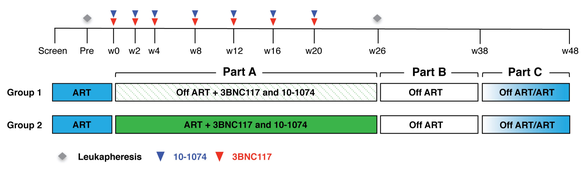

Figure 1. Study design.

Of the 26 enrolled participants, 18 and 8 were randomized to Group 1 or 2, respectively (**Fig.2**). Ten additional individuals on suppressive ART were followed over time in parallel under an observational study for repeated blood donations and reservoir assessments while remaining on suppressive ART ("ART alone group")

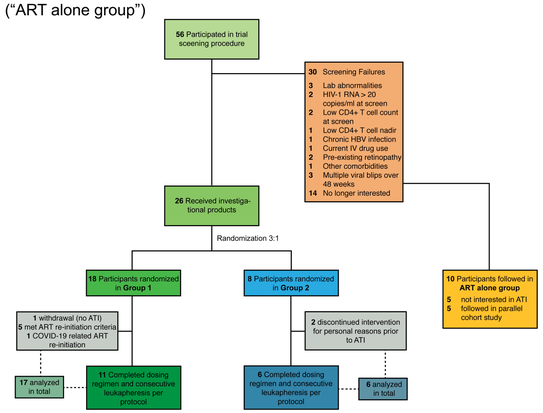

Figure 2. Selection of study participants.

Results:

Repeated antibody infusions over the course of 20 weeks were generally safe and well-tolerated.

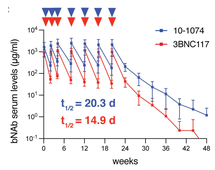

Figure 3. Pharmacokinetics.

Serum concentrations of 3BNC117 and 10-1074 were measured by a bNAb-specific pseudovirus neutralization assay and showed average half-lives of 14.9 and 20.3 days, respectively (**Fig.3**). There was no significant difference in antibody half-lives in the absence (Group 1) or presence of ART (Group 2).

Thirteen out of 17 (76%) evaluable Group 1 participants maintained viral suppression for at least 20 weeks after ART discontinuation (**Fig.4**).

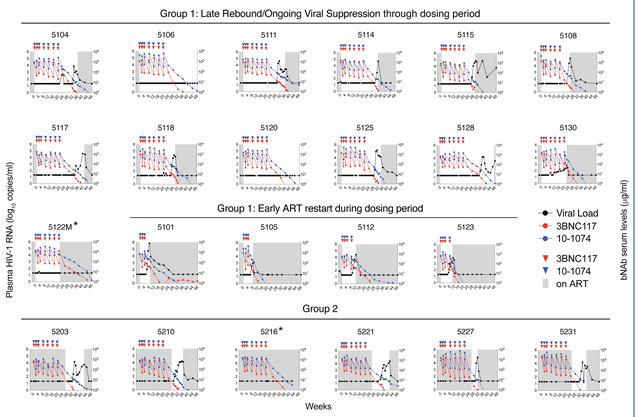

Figure 4. Virological and pharmacokinetic follow-up of individual participants.

For 16 Group 1 participants who did not re-initiate ART before rebound, repeated combination antibody therapy was associated with viral suppression for a minimum of 7 weeks with a median time to rebound of 28.5 weeks. Although the overall time to rebound was significantly longer than individuals that received only 3 infusions of the same antibodies in a previous clinical trial[1] (**Fig.5,** *left panel*), the time to rebound after the last infusion was similar (**Fig.5,** *right panel*).

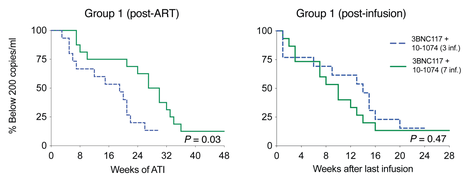

Figure 5. Kaplan-Meier plots summarizing time to viral rebound after ART discontinuation (*left panel*) or after last antibody infusions (*right panel*).

Two of the Group 1 participants (5106 and 5120) completed study follow-up at 48 weeks without experiencing rebound. Individuals that remained suppressed after week 20 only experienced viral rebound after the serum concentration of 3BNC117 decreased below approximately 10 µg/ml, resulting in a period of 10-1074 monotherapy.

To examine the potential impact of viral monoclonal antibody sensitivity testing on time to viral rebound, we performed post-hoc analyses of reservoir viruses (**Fig. 6**).

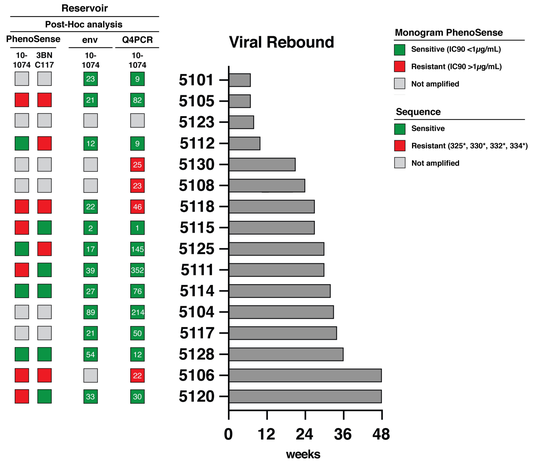

Figure 6. Post-hoc phenotypical and genotypical sensitivity analysis of reservoir viruses and impact on time to viral rebound. Bar graphs depict time to viral rebound in ascending order. Number in the squares depict the number of analyzed sequences.

Envelope (env) sequences were obtained from the reservoir by limiting dilution PCR and Q4PCR[2,3]. Env sequences were subsequently analyzed for known 10-1074 resistance mutations and categorized as sensitive or resistant. The samples were also analyzed for resistance to 10-1074 and 3BNC117 by the PhenoSense Monoclonal Antibody (mAb) Assay (Labcorp-Monogram Biosciences) with an exploratory susceptibility threshold (IC90 1 µg/ml). In this small data set, both genotypic and phenotypic sensitivity analyses failed to predict clinical outcome and time to viral rebound.

To examine the effect of prolonged bNAb therapy on the latent reservoir, we performed Q4PCR[2,3] on samples obtained approximately 2-4 weeks before and 26 weeks after the first antibody infusion. In addition, we assayed the reservoir in the parallel group of 10 participants that remained on suppressive ART without receiving antibody infusions at paired time points with a median interval of 32 weeks (range 24 to 58 weeks) between baseline and follow-up. Overall, we recovered and analyzed 6074 defective (bNAb Therapy n=3866, ART alone n=2208) and 841 intact proviral (bNAb Therapy n=542, ART alone n=299) sequences (**Fig.7**)

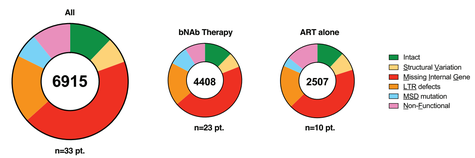

Figure 7. Pie charts show the distribution of recovered intact and defective proviral sequences. Categories of proviral subtypes are depicted according to color legend.

There was no overall change in the absolute number of defective proviruses in the reservoir during the observation period in either the active therapy or parallel ART alone group (**Fig.8,** *left*). In addition, there was no significant change in the relative representation of the 5 different categories of defective proviruses in the active or parallel ART alone group (**Fig.8,** *right*).

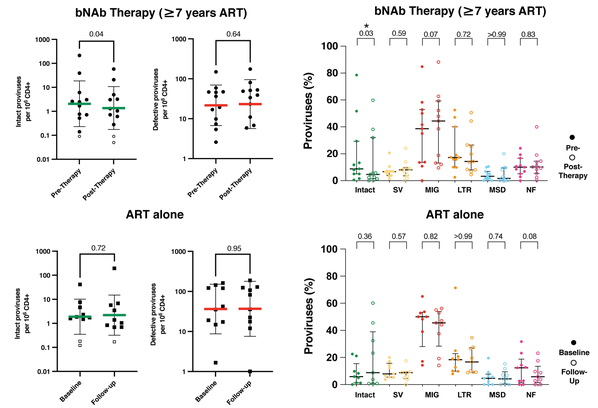

Figure 8. Reservoir quantification and composition. Frequency of intact and defective proviral genomes (*left*) and longitudinal changes in relative representation of proviral subtypes (*right*) for bNAb Therapy ≥ 7 years ART (participants that have been on ART for at least 7 years, *upper panel*) and ART alone (*lower panel*) groups. Categories of proviral subtypes abbreviated and colored as shown in *Fig. 7*.

In contrast to the defective proviruses, there was a moderate but significant change in both the absolute number and relative representation of intact proviruses in the antibody treated participants who had been on suppressive ART for at least 7 years. Additional larger and longer studies will be required to define the precise half-life of the intact reservoir during antibody therapy

Conclusions:

- **Prolonged viral suppression** with **repeated antibody infusions** of **3BNC117** and **10-1074**
- **Post-treatment control** (>48 weeks) in **two study participants**
- **Viral rebound** after **one** of the **antibodies** reached **sub-therapeutic** serum **concentrations** (below 10 µg/ml)
- **Phenotypic** and **genotypic sensitivity analysis unable** to **predict time** to **viral rebound**
- **Immunotherapy** with **3BNC117** and **10-1074** is **associated** with **significant changes** in the **size** and **composition** of the **intact** proviral **reservoir without** measurable **effect on** the **defective reservoir**
- **Larger** and **longer studies required** to **define** the precise **half-life** of the **intact reservoir** during **antibody therapy**

References:

1. Mendoza et al. (2018) *Nature* 10.1038/s41586-018-0531-2
2. Gaebler et al. (2019) *J Exp Med* 10.1084/jem.20190896
3. Gaebler, Falcinelli et al. (2021) *J Virol* 10.1128/JVI.01986-20

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