An Exploratory Study of Combination Therapy with 3BNC117 and 10-1074 in HIV-Infected Individuals

Protocol Short Title: Dual bNAb

NIAID Protocol Number: 18-I-0115

Sponsored by: **National Institute of Allergy and Infectious Diseases (NIAID)**

IND Sponsor: **Office of Clinical Research Policy and Regulatory Operations**
Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health

IND #: 139654

3BNC117 provided by Celldex Therapeutics
10-1074 provided by Massachusetts Biotechnology Council (MassBio, Inc).

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Draft or Version Number: **3.0**
Version date: **March 19, 2020**

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AR	adverse reaction
ART	combination antiretroviral therapy
AST	aspartate aminotransferase
ATI	analytical treatment interruption
bNAb	broadly neutralizing monoclonal antibody
CFR	Code of Federal Regulations
CRIMSON	Clinical Research Information Management System of the NIAID
CSO	Clinical Safety Office
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCV	Hepatitis C virus
hu-mice	humanized mice
IB	investigator's brochure
ICH	International Conference for Harmonisation
IND	investigational new drug
IRB	institutional review board
IV	intravenous
mAb	monoclonal antibody
NHP	non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections
PI	principal investigator
SAE	serious adverse event/serious adverse experience
SAR	suspected adverse reaction
UP	unanticipated problem
UPnonAE	unanticipated problem that is not an adverse event

PROTOCOL SUMMARY

Full Title:	**An Exploratory Study of Combination Therapy with anti-HIV bNAbs 3BNC117 and 10-1074 in HIV-Infected Individuals**
Short Title:	Therapeutic combination bNAb
Clinical Phase:	1
IND Sponsor:	Office of Clinical Research Policy and Regulatory Operations
Conducted by:	National Institute of Allergy and Infectious Diseases Laboratory of Immunoregulation
Principal Investigator:	Michael C. Sneller, MD
Sample Size:	N= 45
Accrual Ceiling:	50
Study Population:	HIV-infected adults 18-65 years of age
Accrual Period:	18 months
Study Design:	An exploratory, triple-arm study of 3BNC117 plus 10-1074 in subjects with HIV infection
Study Duration:	3 years (June 2018 to June 2021)
Study Agent/ Intervention Description:	3BNC117 30 mg/kg plus 10-1074 30 mg/kg
Primary Objective:	To evaluate safety and tolerability of multiple 3BNC117 and 10-1074 doses
Secondary Objective:	To evaluate the efficacy of 3BNC117 and 10-1074 as determined by its effect on plasma viremia in subjects not taking ART and viral rebound following discontinuation of ART in subjects who began ART during primary HIV infection
Exploratory Objectives:	To investigate whether 3BNC117 and 10-1074 -mediated suppression of HIV replication in the absence of ART allows the development of anti-HIV immunity (i.e., cytotoxic T lymphocyte response). To investigate the capacity of 3BNC117 and 10-1074 to neutralize replication-competent HIV prior to and following administration of the study drugs. To examine and characterize ex vivo 3BNC117 and 10-1074-escape mutants that might develop during the study.

Endpoints:

The rate of occurrence of grade 3 or higher AEs, including SAEs, that, per standard criteria (see safety Section 12.3.1) are probably or definitely related to the test article.

Number of subjects who experience rebound of plasma viremia and meet criteria to restart ART before study week 28. (Cohort 1)

The number of subjects in Cohort 2 who achieve stable suppression of viremia with 3BNC117 plus 10-1074 by study week 28.

PRÉCIS

Recent advances in antibody cloning technologies have led to the discovery of a number of highly potent and HIV-specific broadly neutralizing monoclonal antibodies (bNAbs) from B cells of HIV-infected individuals. It has been shown that certain bNAbs can prevent acquisition of the virus, suppress viral replication, delay and/or prevent plasma viral rebound following treatment interruption in Simian Immunodeficiency virus (SIV)-infected animals and block cell-to-cell transmission of laboratory-adapted HIV *in vitro*. In light of these encouraging outcomes, a number of clinical trials have been conducted in recent years in order to explore the feasibility of achieving sustained virologic suppression using a single bNAb in HIV-infected individuals following analytical treatment interruption (ATI). Despite the fact that repeated administration of a single bNAb was safe and well-tolerated, the vast majority of study subjects experienced plasma viral rebound following ATI, clearly demonstrating that successful passive immunotherapy will require different approach, including the use of a combination of 2 or more bNAbs to achieve extended periods of virologic suppression.

Given a major emphasis on current HIV research lies in the possibility of achieving ART-free virologic remission, it is of great interest to investigate whether a combination of potent HIV-specific bNAbs, such as 3BNC117 and 10-1074, can prevent plasma viral rebound in infected individuals upon discontinuation of ART or suppress viral replication in subjects who are not taking ART.

1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

Prolonged suppression of plasma viremia is now achievable in the majority of HIV-infected individuals receiving combination antiretroviral therapy (ART). Consequently, ART has dramatically improved the clinical outcome of infected individuals. However, complete eradication of HIV has not been possible using ART alone and plasma viremia rapidly rebounds in virtually all chronically HIV-infected individuals upon cessation of therapy[1]. Multiple studies have demonstrated that HIV persists in latently infected, resting $CD4^+$ T cells of infected individuals receiving clinically effective doses of ART[2-4]. Persistence of the HIV reservoirs carrying replication-competent virus despite suppression of plasma viremia with ART is considered to be the major obstacle to the eradication of HIV.

Despite the success of ART in suppressing HIV replication and plasma viremia, the burden of taking daily medication for life, long-term toxicity of ART, and the potential for developing resistance to antiretroviral drugs necessitates a continued search for effective alternatives for achieving durable control of HIV replication in infected individuals. Consequently, a major thrust of HIV research over the past decade has been to develop therapeutic strategies that can control HIV replication in the absence of ART. One such strategy is to provide passive immunization via neutralizing monoclonal antibodies (mAbs) against HIV.

Research directed at potential pathways towards the development of an effective HIV vaccine has provided insights into the nature of the immune response to HIV infection[5,6]. Recent advances in antibody cloning technologies and B cell biology have led to the discovery of several highly potent and broadly neutralizing mAbs (bNAbs) against HIV produced by B cells of select HIV-infected individuals. These bNAbs effectively neutralize infectivity of the majority of existing HIV-1 isolates *in vitro*[7-9].

Pre-clinical studies in Rhesus macaques have demonstrated that monotherapy with bNAbs can induce transient suppression of plasma viremia with subsequent rebound due to the emergence of bNAb-resistant isolates[10]. Administration of combinations of bNAbs targeting non-overlapping epitopes of HIV gp120 can provide prolonged control of active infection in humanized mice (hu-mice) and primate models[10-12]. In a recent pre-clinical study in an acute SHIV-macaque model, the combination of two bNAbs (10-1074 and 3BNC117) targeting non-overlapping epitopes of HIV was able to induce prolonged control of viremia that persisted after discontinuation of therapy[13]. Several effector mechanisms are potentially involved in suppression of HIV/SHIV viremia by bNAbs including; accelerated clearance of free virons[14], enhanced clearance of infected cells[15,16], augmentation of host humoral immunity[17], and induction of potent antiviral $CD8^+$ T cell immunity[13].

Initial Phase I studies with bNAbs in ART naïve HIV-infected individuals have shown bNAbs are well-tolerated and capable of transiently suppressing viremia by 0.8-1.0 $\log_{10}$[18-20]. The results from these Phase I safety studies led to three trials that addressed the effect of multiple doses of a single bNAb on plasma viral rebound in HIV-infected individuals undergoing analytical treatment interruption (ATI). Two trials of VRC01 and one trial of 3BNC117, bNAbs that target the same CD4-binding epitope on gp120, have been completed and published[21,22]. In all three studies, bNAb treatment was observed to significantly delay, but not prevent plasma viral rebound following ATI[21,22]. Emergence of VRC01 or 3BNC117 resistant HIV after infusions of the respective bNAbs and discontinuation of ART was observed in all three trials. Of note,

rebounding virus in these studies remained sensitive to bNAbs (such as 10-1074) that target different epitopes of HIV gp120. Taken together, these findings suggest that successful immunotherapy will probably require treatment with two or more bNAbs that target different sites on the HIV envelope glycoprotein. Thus, it is of interest to investigate whether a combination of two potent bNAbs that target different epitopes of the CD4 binding site on HIV gp120, can prevent plasma viral rebound in infected individuals upon discontinuation of ART. Furthermore, it is of considerable interest to explore the possibility of achieving sustained virologic remission and induction of long-lasting anti-HIV immunity in individuals with relatively low levels of plasma viremia who are not taking ART.

1.1.1 Description of the Study Agents

3BNC117 is a recombinant, fully human mAb of the IgG1κ isotype that specifically binds to the CD4 binding site on the HIV-1 Env gp120. 3BNC117 was isolated at the Rockefeller University, cloned and expressed in Chinese hamster ovary (CHO) cells (clone 5D5-5C10), and purified using standard methods.

3BNC117 Drug Product, manufactured under Current Good Manufacturing Practice (CGMP) by Celldex Therapeutics, is formulated as a sterile solution intended for single-use parenteral administration. Each vial contains 20 mg/ml 3BNC117 protein in 5 or 10 ml volume of buffered solution. Additional details on the 3BNC117composition and manufacturing can be found in the 3BNC117 Investigators Brochure (IB), v4.0 Mar. 2017.

10-1074 is a recombinant, fully human mAb of the IgG1λ isotype that specifically binds to the base of the V3 loop within HIV-1 envelope gp-120. 10-1074 was isolated from an HIV-infected individual with high titer serum neutralization activity. The mAb was generated by cloning the heavy and light chain variable regions isolated from a single memory B cell. 10-1074 was isolated at the Rockefeller University, cloned and expressed in CHO cells (clone 3G4), and purified using standard methods.

10-1074 Drug Product, manufactured under CGMP by MassBio, is formulated as a sterile solution intended for single-use parenteral administration. Single-use vials contain 10 or 30 ml of 10-1074 at a 20 mg/ml concentration.

1.1.2 Summary of Pre-Clinical Studies

3BNC117

A tissue cross-reactivity study, performed on a full panel of tissues from humans and rats, showed good concordance of binding between the two species. 3BNC117 showed widespread cytoplasmic binding, however it is generally understood that cytoplasmic binding is considered of little to no toxicologic significance. Membrane binding of 3BNC117 was restricted to two limited/rare cell types in conjunctival recesses and in the urinary bladder (neither of which correlated with findings in the repeat dose toxicology study).

3BNC117 was evaluated for safety in a multi-dose study in rats. 3BNC117 was well-tolerated and despite some animals producing anti-drug antibodies, the rats appeared to have maintained adequate drug exposure in the study with twice per week dosing for four weeks. No significant adverse findings were noted. Specifically, aside from injection site findings, there were no 3BNC117-related effects on clinical observations, body weight, food consumption, body

temperature, clinical pathology parameters, organ weights or macroscopic and microscopic observations, and the NAOEL was determined to be the high dose of 60 mg/kg twice a week for four weeks (3BNC117 Investigators Brochure, v4.0 Mar. 2017).

10-1074

A GLP-compliant tissue cross-reactivity study, performed on a full panel of tissues from humans and rats, showed concordance of binding, with some exceptions, between the two species. While 10-1074 showed cytoplasmic binding in some tissues (mononuclear leukocytes, liver, pituitary, placenta, and optic nerve), it is generally understood that cytoplasmic binding is considered of little to no toxicologic significance. The antibody 10-1074 was evaluated for safety in a GLP-compliant multidose study in rats. The test article 10-1074 was well tolerated when administered by the intravenous (IV) or subcutaneous (SC) routes, with the majority of findings likely associated with the immune response to the human protein in the rat, or injection site inflammation. It was concluded that the no-observed-adverse-effect-level (NOAEL) was the high dose level (60 mg/kg/injection, twice weekly, for four weeks) for all routes of administration (10-1074 Investigators Brochure, v3.0 Aug. 2017).

Summary of antiviral activity of 3BNC117 and 10-1074 in animal models

- When a combination of ART and 3BNC117 were administered together, plasma HIV-1 RNA levels were suppressed to levels below detection in the majority of hu-mice tested. Importantly, continued therapy with 3BNC117 alone was able to maintain virologic suppression, as long as 3BNC117 plasma levels remained above 1 µg/ml[23].

- A combination immunotherapy with 3BNC117 and two other broadly neutralizing antibodies that target different sites on HIV-1 gp120, PG16 and 10-1074, successfully controlled HIV-1 infection in hu-mice by reducing both plasma viral RNA and cell-associated viral DNA[23].

- 3BNC117 administered as a single infusion of 5 mg/kg protected non-human primates (NHPs) from infection by an intrarectal challenge with $SHIV_{AD8EO}$ or $SHIV_{CL7AD8}$ (1,000 TCID50)[10,24] .

- A single dose of 3BNC117 and 10-1074, each at 10mg/kg, led to suppression of $SHIV_{AD8EO}$ plasma viremia to undetectable levels in 4 out of 5 non-human primates (NHPs) tested. Virologic suppression lasted 18 to 36 days, and plasma viremia subsequently rebounded to pretreatment levels. Suppression of $SHIV_{AD8EO}$ viremia was maintained until a threshold plasma mAb concentration of approximately 5 µg/ml was reached. Analysis of emerging virus populations in the 5 long-term chronically infected macaques revealed no obvious genetic changes affecting sensitivity to 3BNC117[10].

- A 14-day course of 3BNC117 and 10-1074 administered to rhesus macaques beginning on day 3 after infection with $SHIV_{AD8EO}$ resulted in sustained suppression of plasma viremia for 56-177 days. Depletion of $CD8^+$ T cells led to rapid return of viremia, suggesting the bNAb treatment resulted in development of potent $CD8^+$ T cell immunity capable of controlling of viremia[13].

1.1.3 Summary of Relevant Clinical Studies

1.1.3.1 3BNC117 Clinical Studies

Protocol MCA-0835
This protocol was an open label, dose-escalating, first-in-human phase 1 study to evaluate safety, pharmacokinetics (PK) and antiretroviral activity of 3BNC117 in HIV-uninfected and HIV-infected subjects. HIV-infected subjects were either on or off ART at the time of enrollment with HIV-1 viral loads <100,000 copies/ml and absolute $CD4^+$ T cell counts of >300 cells/µL. Study subjects were administered one or two intravenous infusions of 3BNC117 at one of four increasing dose levels (1 mg/kg, 3 mg/kg, 10 mg/kg and 30 mg/kg) and were followed for 24 weeks after the last 3BNC117 administration.

In total, 55 subjects (22 HIV-uninfected as well as 17 viremic and 16 ART-treated HIV-infected individuals) enrolled in the study. Five HIV-uninfected individuals received two infusions of 3BNC117 at 30 mg/kg, 12 weeks apart. Twenty-two subjects (3 HIV-uninfected and 19 HIV-infected) were administered one dose of 30 mg/kg. 3BNC117 was generally safe and well-tolerated at the doses tested. No grade 3 or 4 adverse events (AEs), or serious adverse events (SAEs) deemed at least possibly related to 3BNC117 nor any clinically significant treatment related changes in laboratory parameters occurred during study follow-up.

In total, 221 AEs were reported during the study, and 70 were considered at least possibly related AEs. Of the possibly related AEs, 59 (84%) were graded mild and 11 (15%) were graded moderate. The most commonly reported related AEs were headache and malaise or fatigue, which were transient and mild in severity in the majority of cases[18].

Protocol MCA-0867[22]
This protocol was an open label, phase 2a study to evaluate the safety and antiretroviral activity of two or four 3BNC117 infusions in HIV-infected subjects on combination ART during a brief analytical treatment interruption (ATI). Study subjects were administered two 30 mg/kg intravenous infusions of 3BNC117 at weeks 0 and 3 (group A), or four infusions at weeks 0, 2, 4 and 6 (group B). ART was discontinued 2 days after the first 3BNC117 infusion. Subjects were followed weekly and ART was resumed if viral rebound occurred (HIV-1 RNA >200 copies/ml in 2 consecutive measurements) or $CD4^+$ T cell counts declined to <350 cells/µl. Subjects were followed for a total of 9 months after the first 3BNC117 infusion.

Sixteen subjects enrolled and follow up was completed on January 25, 2017. 3BNC117 showed similar safety profile as in protocol MCA-835, and was generally safe and well tolerated in both study groups A and B. No grade 3, 4 or SAEs deemed at least possibly related to 3BNC117 and no clinically significant treatment-related changes in laboratory parameters have occurred during study follow-up. In total, 56 AEs were reported and 25 were considered at least possibly related to 3BNC117. Most reported AEs were grade 1 (n=44). Overall, the most commonly reported AEs were headache and upper respiratory tract infection.

All enrolled subjects reinitiated ART after viral rebound and achieved viral suppression. None of the subjects experienced symptoms consistent with acute retroviral syndrome at the time of viral rebound.[22]

Protocol MCA-0866
HIV-infected subjects on ART were administered four 3BNC117 infusions at 30 mg/kg at weeks 0, 12, 24 and 27. ART was discontinued at week 24 and subjects were followed weekly to monitor

plasma HIV-1 RNA levels. ART was reinitiated upon viral rebound as in protocol MCA-867 (see above). A total of 17 subjects enrolled in this study and follow up after ART re-initiation is ongoing.

In this study, subjects were not selected based on pre-existing sensitivity to 3BNC117. The observed median time to viral rebound (first plasma HIV-1 RNA level > 200 copies/ml) was 4 weeks (range: 2 – 17 weeks).

In summary, 3BNC117 was generally safe and well-tolerated in these three clinical trials. The most commonly reported AEs were mild headache (18%), malaise/fatigue (15%), nausea (11%) and flu-like symptoms (10%). Approximately 6% of subjects reported mild ophthalmologic complaints (such as pruritus, conjunctival erythema, increased lacrimation, or blurry vision) during study follow up of 6 to 9 months, but a causal relationship with 3BNC117 was not established. No SAEs or grade 3 or 4 AEs deemed related to 3BNC117 occurred.

1.1.3.2 10-1074 Clinical Studies

10-1074 was evaluated in a phase 1 study in both HIV-uninfected and HIV-infected individuals (protocol MCA-885)[19]. Study subjects were administered one intravenous infusion of 10-1074 at increasing dose levels (3 mg/kg, 10 mg/kg or 30 mg/kg) and were followed for 24 weeks after infusion.

A total of 33 study subjects enrolled in the study (14 HIV-uninfected and 16 viremic and 3 ART-treated HIV-infected individuals) received 10-1074. Of these, 21 received one infusion of 30 mg/kg. 10-1074 was generally safe and well-tolerated. A total of 57 AEs was reported during a follow-up period of 6 months, 88% of these were of grade 1 severity. The most commonly reported AE deemed possibly related to the study drug was transient, mild headache. There were no SAEs or grade 3 related AEs. A safety data summary is included in the 10-1074 Investigator's Brochure (IB).

Thirteen viremic subjects received 10-1074 at 30 mg/kg. Eleven of these subjects were 10-1074-sensitive and showed a rapid decline in viremia by a mean of 1.52 $\log_{10}$ copies/ml. Virologic analysis revealed the emergence of 10-1074-resistant viruses in the first weeks after infusion. Emerging escape variants carried mutations in known contact sites (N332, N334 and D/N425) and were generally resistant to the related V3-specific antibody PGT121, but remained sensitive to antibodies targeting non-overlapping epitopes, such as the anti-CD4-binding-site antibodies, 3BNC117 and VRC01[19].

1.1.3.3 3BNC117 and 10-1074 in combination

Two phase 1 clinical trials of the combination of 3BNC117 plus 10-1074 are currently underway. In one study (protocol YCO-0899), HIV-uninfected individuals received 1-3 doses of the antibody combination at 3 or 10 mg/kg versus placebo administered intravenously. Twenty-four subjects have enrolled and all antibody infusions have been administered. Follow-up is ongoing and study assignment remains blinded.

In the second study (protocol MCA-0906), HIV-infected individuals on or off ART received 1 to 3 doses of 3BNC117 plus 10-1074 at 10 or 30 mg/kg each or placebo. To date, 29 individuals

enrolled (25 received the antibody combination and 4 received placebo) in this study; eight have received 3 infusions of 30 mg/kg, administered 3 weeks apart.

There have been no SAEs, and the safety profile of the combination of 3BNC117 plus 10-1074 is similar to what was observed with either antibody alone (Appendix A). The estimated half-lives of 3BNC117 and 10-1074 in HIV-uninfected individuals when given in combination are similar to what was observed when the antibodies were administered individually, i.e. 18 days for 3BNC117 and 24 days for 10-1074.

To date, the combination of 3BNC117 and 10-1074 appears to be well tolerated and able to delay viral rebound in the absence of ART (protocol MCA-0906). In MCA-0906, subjects discontinue ART two days after the first infusions of 3BNC117 and 10-1074 (week 0) and receive two additional combination antibody infusions at weeks 3 and 6. Of 12 subjects enrolled in the treatment interruption group of the study, one subject experienced viral rebound at week 5, while viral rebound occurred at 15, 19, 20 and 21 weeks in the other 4 subjects. The remaining 7 enrolled subjects continue to maintain suppression for 2 to 14 weeks following ART discontinuation.

1.1.3.4 Summary of Clinical Studies with 3BNC117 and/or 10-1074

In aggregate, the clinical experience with >160 subjects who have received infusions of either 3BNC117 or 10-1074 alone or in combination, indicates that the antibodies are generally safe and well-tolerated and the majority of reported AEs were transient and of grade 1 severity. No SAEs considered at least possibly related to either 3BNC117 or 10-1074 have been reported to date. Preliminary data show that the combination of 3BNC117 and 10-1074 demonstrate the same safety and pharmacokinetic profiles as each antibody administered alone. In addition, available antiviral activity data suggest that the combination can further delay viral rebound following discontinuation of ART, in comparison to 3BNC117 alone.

1.2 Rationale

The objectives of this study are to evaluate the safety and virologic efficacy of multiple doses of 3BNC117 and 10-1074 in two groups of HIV-infected individuals. Group 1 will enroll ART-treated subjects who began therapy during primary HIV infection. Individuals who began ART during primary HIV infection exhibit less viral diversity within their reservoir of persistently infected $CD4^+$ T cells[25,26] and are thus, less likely to harbor HIV quasispecies resistant to neutralization by 3BNC117 or 10-1074. A second rationale for limiting Group 1 to individuals who began ART during primary infection is to investigate whether treatment with 3BNC117 plus 10-1074 results in long-term suppression of plasma viremia in the absence of both ART and mAb treatment, as was observed in the SHIV primate study described in Section 1.1.2[13]. Subjects in Group 1 will be randomized into two arms; mAb treatment (3BNC117 plus 10-1074) or placebo. The use of a placebo arm in Group 1 is necessary as a significant proportion of individuals who began ART during primary infection will maintain viral suppression, in the absence of any intervention, for at least 6 months following discontinuation of ART[27,28].

Group 2 will enroll individuals with HIV viremia who are not receiving ART. Inclusion of this group will allow us to investigate the antiviral activity of the study mAbs in subjects with stable viremia in the absence of recent ART. Furthermore, the feasibility of achieving sustained

virologic remission and induction of long-lasting anti-HIV immunity in individuals with relatively low levels of plasma viremia who are not taking ART will be addressed in this group.

The efficacy of treatment with this bNAb combination will be determined by its effect on viral rebound following discontinuation of ART in Group 1 and on plasma viremia in Group 2.

The rationale for using the proposed dose of 3BNC117 and 10-1074 is based on the safety and pharmacokinetic data generated from Phase I human studies[18,19,22].

Analytical Treatment Interruption (ATI)
Various laboratory-based assays measuring the frequency of infected $CD4^+$ T cells carrying HIV proviral DNA and/or replication-competent virus and HIV-specific immune responses have been used to assess efficacy of immune-based therapies. To date, none of the assays are clinically validated to predict actual antiviral efficacy *in vivo*. Thus, ATI has been used to evaluate the antiviral efficacy of immune-based therapies by testing the ability of these interventions to blunt or prevent the viral rebound that occurs following interruption of ART. The use of ATI in the design of this study (Group 1) is the only way to determine if administration of 3BNC117 and 10-1074 results in clinically relevant antiviral activity in antiretroviral-treated individuals, as evidenced by an attenuated or absent plasma viral rebound following interruption of ART. ATI, with frequent clinical and laboratory monitoring along with strict criteria for re-initiation of ART, is a safe and acceptable strategy to evaluate the efficacy of 3BNC117 and 10-1074 in this population of antiretroviral-treated HIV-infected adults. This is supported by the results from current and prior studies of immune based therapy using ATI to assess virologic efficacy[21,22,28-33], as well as a subgroup analysis of the SMART study[34].

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate safety and tolerability of multiple doses of 3BNC117 combined with 10-1074 in HIV-infected individuals.

2.2 Secondary Objective

To evaluate the antiviral effect of combination therapy with 3BNC117 and 10-1074.

2.3 Exploratory Objectives

- To investigate whether 3BNC117 and 10-1074 -mediated suppression of HIV replication in the absence of ART allows the development of anti-HIV immunity (i.e., CTL response).
- To investigate the capacity of 3BNC117 and 10-1074 to neutralize replication-competent HIV prior to and following administration of the study drugs.
- To examine and characterize ex vivo 3BNC117 and 10-1074-escape mutants that might develop during the study.

3 STUDY DESIGN

3.1 Description of the Study Design

The proposed trial will be a triple-arm study to examine the effect of 3BNC117 combined with 10-1074 in two groups of HIV-infected individuals. In Group 1, 30 individuals who began ART during primary HIV-1 infection will be randomized 1:1 to treatment with 3BNC117 plus 10-1074 or normal saline placebo. Study staff and participants will be blinded to Group 1 treatment assignments. Efficacy will be measured in this group by comparing the number of subjects in the treatment and placebo arm who meet criteria to restart ART during the ATI-treatment phase of the study (weeks 0-28).

For study Group 2, up to 15 viremic individuals not taking ART will receive 3BNC117 combined with 10-1074. Efficacy will be measured in this group by the proportion of subjects in whom mAb treatment is able to suppress plasma viremia during the treatment phase (weeks 0-28). Study subjects will receive infusions of 3BNC117 (30mg/kg) and 10-1074 (30mg/kg) or placebo (Group 1) at study days 0, Week 2, Week 4, and every four weeks thereafter for up to 24 weeks (Figure 1).

Analytical treatment interruption (ATI)
After study day 3, all subjects in **Group 1** will stop ART to determine if treatment with 3BNC117 and 10-1074 can prevent plasma viral rebound. Individuals taking non-nucleoside reverse transcriptase inhibitors (NNRTIs) will switch to a protease or integrase inhibitor-based regimen at least 2 weeks prior to week 0 to ensure that the washout period of antiretroviral agents is roughly equal. During the ATI/Treatment phase of the study, HIV RNA levels and $CD4^+$ T cell counts will be monitored every 2 weeks.

Group 1 subjects will be instructed to restart ART if they meet one or more of the following criteria during the ATI phase:

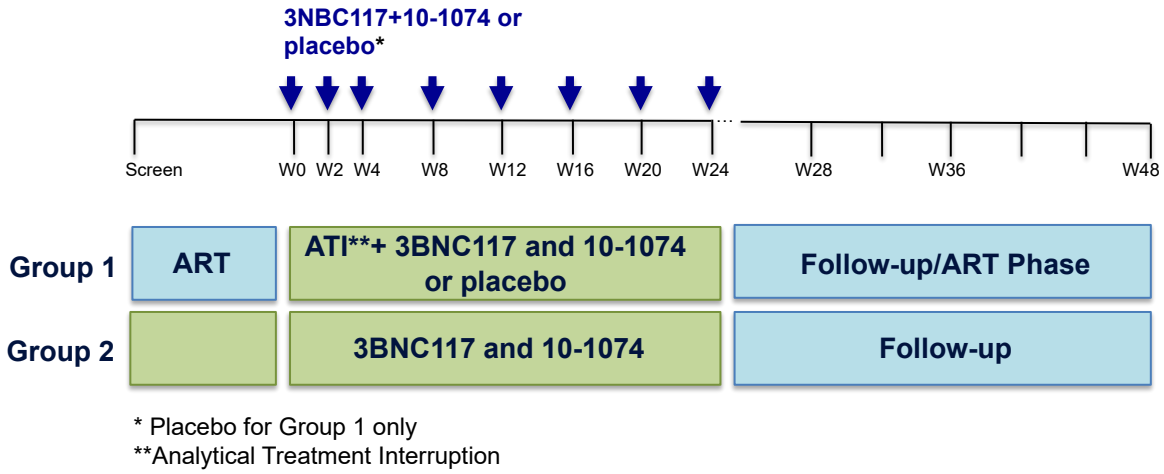
- A confirmed >30% decline in baseline $CD4^+$ T cell count or an absolute $CD4^+$ T cell count <350 cells/mm^3 that is associated with a HIV RNA level >40 copies/ml.
- A sustained (>4 weeks) HIV RNA level of >1,000 copies/mL
- Any HIV-related syndrome (e.g. acute retroviral syndrome, opportunistic infection)
- Pregnancy

Subjects who meet one or more of the above criteria during the ATI/Treatment Phase will not receive additional antibody/placebo infusions and enter the follow-up phase (Figure 1). Subjects who have not met criteria to restart ART by week 28 may continue the ATI and have HIV RNA levels and $CD4^+$ T counts monitored every 2 weeks until they either meet criteria to restart ART or reach study week 64 (see Section 6.4).

Subjects in **Group 2** will have their plasma viremia and $CD4^+$ T counts monitored every 2 weeks and will be removed from the treatment phase of the study if they meet any of the following criteria:

- A confirmed >30% decline in baseline $CD4^+$ T cell count or an absolute CD4 cell count <350 cells/mm^3
- A sustained (>4 weeks) 0.5_{log10} increase in baseline HIV RNA level
- Opportunistic infection
- Pregnancy

Figure 1: Study Outline



* Placebo for Group 1 only
**Analytical Treatment Interruption

3.2 Study Endpoints

3.2.1 Primary Endpoint

The rate of occurrence of grade 3 or higher AEs, including SAEs, that, per standard criteria (see safety Section 12.3.1) are probably or definitely related to the test article.

3.2.2 Secondary Endpoints

Difference between the treatment and placebo arms in the number of subjects in study Group 1 who experience rebound of plasma viremia and meet criteria to restart ART prior to study week 28.

3.2.3 Exploratory Endpoint

Number of subjects in study Group 2 who achieve suppression of viremia to <40 copies/ml by study week 28.

4 STUDY POPULATION

4.1 Recruitment Plan

Subjects will be recruited from existing cohorts of individuals participating in National Institute of Allergy and Infectious Diseases (NIAID) protocols 09-I-0030 and 02-I-0202 who meet the Inclusion/Exclusion Criteria. Additional local and regional recruitment will be done using direct mailing to infectious disease physicians, internet ad campaigns, social media outlets, print ads, and from local clinics via the NIAID patient recruitment contract with Matthews Media Group.

4.2 Subject Inclusion Criteria

General Inclusion Criteria for both Groups

1. Age 18-65 years old.
2. HIV-1 infection and clinically stable.
3. General good health and has an identified primary health care provider for medical management of HIV infection and is willing to maintain a relationship with a primary health care provider for medical management of HIV infection while participating in the study.
4. $CD4^+$ T cell count >450 cells/mm^3 at screening.
5. Laboratory values within pre-defined limits at screening:
    a. Absolute neutrophil count >1,000/mm^3.
    b. Hemoglobin levels >10.0 g/dL for men and >9.0 g/dL for women.
    c. Platelet count >100,000/mm^3.
    d. Estimated or a measured glomerular filtration rate >60 mL/min/1.73m^2 as determined by the National Institutes of Health (NIH) Clinical Center laboratory.
    e. AST and ALT levels of <2.5 x upper limit of normal (ULN), direct bilirubin within the normal range for the NIH Clinical Center laboratory.
6. Willingness to have samples stored for future research.

<u>Inclusion criteria specific for Group 1</u>

7. Institution of ART within 12 weeks of being diagnosed with primary HIV-1 infection
8. *Primary HIV-1 infection* is defined as meeting at least one of the following criteria:
    a. Detectable plasma HIV-1 RNA levels of >2000 copies/mL with a negative result from an HIV-1 EIA, or
    b. Positive result from an HIV-1 EIA with a negative or indeterminate result from an HIV-1 western blot or another confirmatory antibody test that subsequently evolves to a confirmed positive result, or
    c. Negative result from an HIV-1 EIA within the past 4 months and HIV-1 RNA levels of >400,000 copies/mL, in the setting of a potential exposure to HIV-1.
    d. Negative result from an HIV-1 EIA within 6 months prior to a positive result from an HIV-1 EIA and an HIV-1 western blot or another confirmatory antibody test.
    e. Presence of low level of HIV antibodies as determined by having a positive EIA or a positive Western blot with a non-reactive detuned EIA according to a serologic testing algorithm for recent infection[35].
9. Documentation of continuous ART treatment with suppression of plasma viral level below the limit of detection for ≥1 years. Individuals with “blips” (i.e., detectable viral levels on ART) prior to screening may be included provided they satisfy the following criteria:
    a. The blips are <400 copies/mL, and
    b. Succeeding viral levels return to levels below the limit of detection on subsequent testing.

10. Willingness to undergo ATI
11. Willingness for both male and female subjects to agree to use barrier protection methods or abstinence during the ATI phase of the study to decrease the risk of HIV transmission.

Inclusion criteria specific for Group 2

12. No ART within 24 months of screening.
13. HIV plasma viremia between 200 and 5,000 copies/mL at screening AND at least two documented viral level ≥200 copies/mL in the 12 months prior to screening.

At the screening visit, subjects considering enrollment in Group 2 will be advised that current guidelines recommend treatment of all individuals with HIV infection regardless of viral levels and CD4 counts.

Reproductive Risks

Contraception: The effects of 3BNC117 and 10-1074 on the developing human fetus are unknown. For this reason, men and women of childbearing potential must agree to use adequate pregnancy prevention. This includes the use an effective method of contraception (i.e. condom with spermicide, diaphragm with spermicide, hormone-eluting IUD, hormone-based contraceptive with condom) for the study duration. Subjects should also agree to use a male or female condom while off ART. Pregnancy prevention must be practiced continuously for the duration of study participation. Females of childbearing-age must have a negative pregnancy test result prior to receiving each infusion of 3BNC117/10-1074. During the course of the study, if a female subject, or the partner of a male subject suspects or in fact becomes pregnant, the effected subject should inform the study staff immediately, as well as the woman's primary care physician.

4.3 Subject Exclusion Criteria

1. Chronic hepatitis B, as evidenced by a positive test for hepatitis B surface antigen (HBsAg), or chronic hepatitis C virus (HCV) infection, as evidenced by a positive test for HCV RNA. Subjects with a positive test for HCV antibody and a negative test for HCV RNA are eligible.
2. HIV immunotherapy or vaccine(s) received within 1 year prior to screening.
3. Any licensed or experimental non-HIV vaccination (e.g., hepatitis B, influenza, pneumococcal polysaccharide) received within 2 weeks prior to study enrollment.
4. Receipt of other investigational study agent within 28 days of enrollment.
5. Any active malignancy that may require systemic chemotherapy or radiation therapy.
6. Systemic immunosuppressive medications received within 3 months prior to enrollment (Not excluded: [1] corticosteroid nasal spray or inhaler; [2] topical corticosteroids for mild, uncomplicated dermatitis; or [3] oral/parenteral corticosteroids administered for non-chronic conditions not expected to recur [length of therapy ≤10 days, with completion in ≥30 days prior to enrollment]).
7. History or other clinical evidence of:

a. Significant or unstable cardiac or cerebrovascular disease (e.g., angina, congestive heart failure, recent stroke or myocardial infarction).

b. Severe illness, malignancy, immunodeficiency other than HIV, or any other condition that, in the opinion of the investigator, would make the subject unsuitable for the study.

8. Active drug or alcohol use or any other pattern of behavior that, in the opinion of the investigator, would interfere with adherence to study requirements.
9. Pregnancy or breast-feeding at time of screening.
10. Documented multiclass antiretroviral drug resistance that, in the judgment of the investigator, would pose a risk of virologic failure should additional mutations develop during the study (Group 1 only).

Co-enrollment Guidelines: Co-enrollment in other trials is restricted to observational studies or those evaluating the use of a licensed medication and is subject to approval of the principal investigator (PI).

4.4 Justification for Exclusion of Children (Special Populations)

Exclusion of Children:
Children are excluded from this study because there are insufficient data for adults regarding dosing of 3BNC117 and 10-1074 and adverse events to judge the potential risk(s) in children.

4.5 Enrollment of NIH Employees

NIH employees and members of their immediate families may participate in this protocol. We will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the “NIH information sheet on Employee Research Participation.”

For NIH employees:

- NIH staff may be a vulnerable class of subjects.
- Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the participant’s employment or work situation.
- The NIH information sheet regarding NIH employee research participation will be distributed to all potential subjects who are NIH employees.

- The employee subject's privacy and confidentiality will be preserved in accordance with NIH Clinical Center and NIAID policies, which define the scope and limitations of the protections.

- For NIH employee subjects, consent will be obtained by an individual independent of the employee's team. Those in a supervisory position to any employee and co-workers of the employee will not obtain consent.

- The importance of maintaining confidentiality when obtaining potentially sensitive and private information from co-workers or subordinates will be reviewed with the study staff at least annually and more often if warranted.

5 STUDY AGENT/INTERVENTIONS

5.1 Regimen

Both 3BNC117 and 10-1074 will be administered intravenously at 30 mg/kg dose level. Both study groups will receive 8 infusions of 3BNC117 and 10-1074 or placebo (Group 1) at weeks 0, 2, 4, 8, 12, 16, 20, and 24 (see Figure 1). The total duration of therapy is 24 weeks; the duration may be shorter if criteria listed in section 3.1are met.

5.1.1 Formulation, Packaging and Labeling

3BNC117 is provided by Celldex Therapeutics in single-use vials containing 10 ml of 3BNC117 at a 20 mg/ml concentration.

10-1074 is provided by MassBio in single-use vials containing 30 ml of 10-1074 at a 20 mg/ml concentration.

Study agent vials will be individually labeled with the name of the material, volume, lot number, concentration, storage instructions, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

5.2 Study Agent Storage and Handling

3BNC117 and 10-1074 should be stored at 2 - 8°C. Each 3BNC117 vial is single use only. Partially used vials or solutions must not be used to prepare another dose and instead should be handled for destruction according to Clinical Center Pharmacy regulations for the disposal of biological agents.

The site pharmacist must promptly report any storage temperature deviations outside of the normal allowance for the storage device to the PI and the investigational new drug (IND) Sponsor. The product must be quarantined in a separate area. The IND Sponsor's authorized representative will notify the site pharmacist if continued clinical use of the product is acceptable.

5.3 Preparation, Administration, and Dosage of Study Agent

The dose of both 3BNC117 and 10-1074 for this study is 30 mg/kg in 250 mL normal saline with overfill (20 ml). The placebo will be normal saline alone. The two antibodies will be mixed in separate bags of saline for sequential administration. To prepare an IV infusion, the pharmacist will calculate the total milligrams of each antibody needed and add the calculated total milligrams needed to a 250 ml of normal saline with 20 ml overfill using good pharmacy practices to maintain sterility. The infusion solution must be used within 3 hours. Any unused portion of an antibody vial will not be used for another subject.

The antibodies (or normal saline placebo-Group 1) will be administered sequentially by IV infusion (3BNC117/placebo first, followed by 10-1074/placebo). Each infusion will be given over 60 minutes using a volumetric pump and then flush the line with 20 ml normal saline. The total time needed to administer the dose may be longer than 60 minutes based on factors such as subject tolerance.

For women of childbearing potential, study agent administration may not proceed unless a negative pregnancy test has been obtained within the previous 24 hours. Prior to each administration, temperature, blood pressure, heart rate (pulse) and weight will be recorded and a targeted physical examination (based on signs, reported symptoms or interim medical history) may be conducted. Vital signs (temperature, blood pressure, heart rate) will be measured 30 minutes into the infusion and at the end of the infusion. Following the completion of the 10-1074/placebo infusion, the subject will be observed for 30 minutes and vital signs will be taken before the subject leaves the clinic.

5.3.1 Dose Adjustments and Modifications

Mild-moderate infusion related symptoms (Grade I-II), should they develop, will be managed by temporarily stopping the infusion until symptoms have resolved. For symptoms such as fever, myalgia, or urticaria, symptomatic treatment with standard doses of acetaminophen or antihistamines may be given. Once symptoms have resolved, the infusion will be restarted at half the initial rate. If symptoms recur following a reduced infusion rate and symptomatic treatment, the infusion will again be stopped until symptoms resolved and restarted at a lower rate. If the infusion cannot be completed within a 3-hour time frame because of recurrent symptoms, the infusion(s) will be discontinued for that visit.

5.4 Concomitant Medications and Procedures

All concomitant prescription medications taken during study participation will be recorded in CRIMSON. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in CRIMSON are concomitant prescription medications, over-the-counter medications, and non-prescription medications taken at the time of AEs (all grades).

5.5 Prohibited Medications and Procedures

Treatment with immunosuppressive medications during the study is prohibited. Prohibited immunosuppressive medications do not include [1] corticosteroid nasal spray or inhaler; [2] topical corticosteroids for mild, uncomplicated dermatitis; or [3] oral/parenteral corticosteroids given for non-chronic conditions not expected to recur with a length of therapy ≤10 days.

6 STUDY SCHEDULE

For all the study visits, unless otherwise specified, subjects will come to the NIH Clinical Center to undergo the procedures. Unless otherwise specified, the visit window for the post-entry study visits is ± 5 days.

6.1 Screening

Screening may occur over the course of several contacts/visits. All inclusion and exclusion criteria must be assessed within 8 weeks before enrollment, unless otherwise specified in the eligibility criteria.

After signing informed consent, subjects will undergo the following procedures:

- Medical history and physical examination, including weight and vital signs.
- Assessment of concomitant medications
- Blood collection for:
    - HBsAg and Hepatitis C antibody serology
    - Complete blood count (CBC) with differential, PT, activated PTT
    - Chemistry panel to include: alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine, total and direct bilirubin, and serum albumin levels
    - Flow cytometry panel (includes CD4+ cell count)
    - Plasma HIV and HCV viral RNA levels
- Storage of PBMCs, serum and plasma (if needed for repeat HIV antibody testing or viral RNA levels)
- Urinalysis
- Serum or urine pregnancy test for women of child-bearing potential
- Electrocardiogram (ECG)

6.2 Enrollment/Baseline

The enrollment visit may take place over 2 visits to accommodate the baseline pre-treatment apheresis procedure. The first dose of 3BNC117 and 10-1074 or (for Group-1) normal saline placebo will be administered at this visit, and enrollment is defined as the day of receipt of the first study infusions.

Subjects will undergo the following procedures (prior to the first dose of the study antibodies or saline placebo):

- Medical history and physical examination, including weight and vital signs
- Ophthalmologic Exam (within 8 weeks prior to first study infusion)
- Assessment of concomitant medications
- HIV transmission risk behavior assessment and counseling
- Leukapheresis (optional) for research studies
- Blood collection for:
    - Flow cytometry panel (includes CD4+ cell count)
    - Plasma HIV viral RNA levels
    - HLA typing (if not already on file)

  - Storage of plasma, serum and PBMCs
  - CBC with differential
  - Chemistry panels, to include: ALT, AST, ALP, creatinine, total and direct bilirubin, and serum albumin levels
- Serum or urine pregnancy test (for women of child-bearing potential-obtained within 24 hours prior to infusion)

6.3 ATI/Treatment Phase

Subjects will be administered 3BNC117 and 10-1074/ placebo on study day 0. All subjects in Group 1 will discontinue their ART regimen after study day 3. Subsequent infusions of 3BNC117 and 10-1074/placebo will occur at study Week 2, 4, and every four weeks thereafter until study Week 24 for a total of 8 doses (see Figure 1).

Storage of plasma, serum, and cells may be done at study day 0, Week 2, 4 and every 2 weeks thereafter for the duration of the ATI-Treatment phase. Flow cytometry (including CD4 count) and Plasma HIV viral RNA levels will be done every 2 weeks for the duration of the ATI-Treatment Phase. HIV genotype will be obtained on all samples with HIV viral levels >1,000 copies/ml. For select subjects residing outside the local (Bethesda, MD) area, blood samples for blood draw only visits, may be collected at their local clinics or Quest Diagnostics and sent to the NIH Clinical Center for testing. Samples collected at clinics or at Quest may be labeled with a coded identifier, gender, and date of birth, as required by the local facility.

At infusion visits, the following will be done in addition to the flow cytometry panel and plasma HIV viral level:

- Interval medical history and a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each subject
- Assessment of concomitant medications
- Assessment of any new or unresolved AEs/intercurrent illnesses
- Blood collection:
  - CBC with differential
  - Chemistry panels, to include: ALT, AST, ALP, creatinine, total and direct bilirubin, and serum albumin levels
- Serum or urine pregnancy test for women of child-bearing potential (results must be reviewed prior to infusion)

- Optional leukapheresis for research studies will be done at Week 0, 16 and within +/- 14 days of the week 24 infusion
- HIV transmission risk behavior assessment and counseling

For non-infusion visits, participants unable to return to the NIH CC during the COVID-19 epidemic/pandemic due to travel restrictions, blood samples may be collected at their local clinics or Quest Diagnostics and sent to the NIH CC for testing which will include; CBC with differential, plasma HIV viral level, and flow cytometry. Chemistry panels may be run at Quest Diagnostics laboratories and the results sent to the NIH Study team. A study provider (Nurse Practitioner, Physician's Assistant, or Physician) will contact participants by phone and obtain an interval medical history.

After the final infusion at week 24, all subjects in Group 1 will continue to have CD4 counts and plasma viral levels monitored every 2 weeks and will be seen every 4 weeks until they meet criteria to restart ART. If a subject in Group 1 meets criteria for ending ATI prior to Week 24, no further infusions will be given; the subject will be instructed to restart ART and continue to be followed as described in Section 6.4.

If a subject in Group 1 has not met criteria to restart ART at Week 64 but has a sustained viral level >40 copies/ml (but <1,000 copies/ml), s/he will be advised to restart ART. Subjects with sustained VL <40 copies/ml at Week 64 may elect to remain off ART until viremia becomes detectable. For such subjects, CD4 counts and plasma viremia will be monitored every 4 weeks until viremia is detected; at which time they will be instructed to restart ART and be followed as described in Section 6.4 below.

If a subject in Group 2 meets criteria for ending 3BNC117/10-1074 infusions prior to Week 24, they will continue to be followed as described in Section 6.4.

6.4 Follow-up Phase

Group 1: Subjects in Group 1 will enter the follow-up Phase when they meet criteria to re-start ART and will be seen 4, 12, and 24 weeks after restarting ART to ensure viral suppression has been achieved.

Group 2: Subjects in Group 2 will enter the follow-up Phase after their final 3BNC117/10-1074 infusion and will be seen 4, 12, and 24 weeks after the last antibody infusion.

At these visits, subjects in both groups will undergo the following procedures:

- Interval medical history and a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each subject
- Assessment of any new or unresolved AEs or intercurrent illnesses
- Blood collection for:
    - CBC with differential
    - Chemistry panels, to include: ALT, AST, ALP, creatinine, total and direct bilirubin, and serum albumin levels
    - Flow cytometry panel (includes $CD4^+$ T cell count)
    - Plasma HIV viral level
    - HIV genotype (Group 1; if viral level is >1,000 copies/ml)
    - Storage of serum, plasma and PBMCs

Subjects in Group 2 will also have optional blood draw visits for CD4 counts, plasma viral level, and storage at 2, 6, 8, 10, 16, and 20 weeks after the last antibody infusion which may be drawn at NIH or offsite.

For participants who are unable to return to the NIH CC during the COVID-19 pandemic due to travel restrictions, blood samples may be collected at their local clinics or Quest Diagnostics and sent to the NIH CC for testing which will include; CBC with differential, plasma HIV viral level, and flow cytometry. Chemistry panels may be run at Quest Diagnostics laboratories and the

results sent to the NIH Study team. A study provider (Nurse Practitioner, Physician's Assistant, or Physician) will contact participants by phone and obtain an interval medical history.

7 STUDY EVALUATIONS

7.1 Clinical Evaluations

- Subjects will undergo a medical history and physical examination.

7.2 Laboratory Evaluations

7.2.1 Clinical and Research Laboratory Evaluations and Specimen Collection

- HIV viral RNA levels
- HIV genotype (if viral level is >1,000 copies/ml)
- Flow cytometry with $CD4^+$ T cell count
- Routine serologic, hematologic, and clinical chemistry evaluations as described in Section 6

Leukapheresis: Will be performed for research studies including, but not limited to, measurements of the frequency of $CD4^+$ T cells carrying HIV proviral DNA, cell-associated RNA, and replication-competent virus by quantitative co-culture assays. These studies will address the exploratory endpoints. If leukapheresis cannot be performed for technical reasons (e.g., poor venous access), 80 ml of blood will be drawn instead.

Other research evaluations measuring the effect of 3BNC117 and 10-1074 on the HIV pathogenesis may include:

- Frequency of $CD4^+$ T cells carrying HIV proviral DNA and cell-associated HIV RNA
- Levels of cell-associated infectious virus
- Sequencing of viral DNA and RNA
- Neutralization assays using replication-competent HIV against bNAbs
- Frequency of HIV-specific $CD4^+$ and $CD8^+$ T cells
- Markers of T-cell activation, immune exhaustion, and inflammation

8 POTENTIAL RISKS AND BENEFITS

8.1 Potential Risks

General Risks of MAb Treatment

Administration of mAb may have a risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies; however, these reactions are rare and more often associated with mAb targeted to human proteins or with the use of chimeric human-murine mAbs, which would have a risk of human anti-mouse antibodies. Both 3BNC117 and 10-1074 are targeted to a viral antigen and are human mAbs; thus, it is expected these mAbs will have a low risk of such side effects. VRC01, a human bNAb that, like 3BNC117 and 10-1074, targets HIV pp120 has been well tolerated in Phase I/II studies with no safety concerns identified [20,21].

Typically, the side effects of mAbs are mild but may include fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia or chest pain. Most infusion-related events occur within the first 24 hours after beginning administration. Severe reactions, such as anaphylaxis, angioedema, bronchospasm, hypotension and hypoxia, are infrequent and more often associated with mAbs targeted to human proteins or when a nonhuman mAb, such as a chimeric murine mAb, is used.

Delayed allergic reactions to a mAb may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after the exposure to the mAb and is noted to be more common with chimeric types of mAbs.

Analytical treatment interruption (ATI)

The risks from an ATI, performed under close virologic and immunological monitoring are minimal in this subject population. There is a theoretical risk that ATI could lead to the development of HIV drug resistance. This may be a particular concern for individuals taking NNRTIs. However, this potential risk with NNRTIs is essentially eliminated by undertaking the procedures described in Section 3.1[29]. Given the study population, the frequency of immunological and virologic monitoring, and strict criteria for restarting ART, it is extremely unlikely that the ATI will lead to the development of any opportunistic infections or AIDS-defining conditions.

During the ATI phase, subjects may transmit HIV infection if they do not adhere to safe sex practices.

Phlebotomy/Insertion of IV Catheter
This may be associated with discomfort, bruising, local hematoma formation and, on rare occasions, infections, lightheadedness, and fainting.

The amount of blood drawn for research purposes will be within the limits allowed for adult subjects by the NIH Clinical Center (Medical Administrative Policy 95-9: Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf).

Leukapheresis
The potential risks associated with leukapheresis include lightheadedness, dizziness, possible fainting, tingling around the mouth and in the fingers and toes, nausea, chills, vomiting, mild muscle cramps, loss of <1 pint of blood, or pain, bruising, or discomfort at the needle insertion sites. More serious, but rare, complications include nerve damage at the needle insertion site, seizures and air embolism. Most procedures are performed without an incident. Blood components removed during leukapheresis are generally replaced by the body within a few hours or a few days. No infections associated with this procedure have been reported in thousands of cases performed over the last 10 years at the NIH.

HLA typing

Some HLA types have been associated with an increased risk of certain diseases like arthritis and other rheumatologic disorders, or a faster progression to AIDS. HLA typing will be performed on samples collected from all the enrolled subjects. Results from the HLA typing will become part of each subject's medical record at NIH. Medical records containing this information are maintained in a secure place.

8.2 Potential Benefits

Study subjects may not receive direct health benefit from study participation or study infusions. Others may benefit from knowledge gained in this study that may aid in the development better HIV treatments.

9 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

- **Intended Use:** Stored blood samples and data collected under this protocol may be used to study the effect of bNAb treatment and ATI on the virologic and immunologic parameters listed in Section 7.2.1. Samples may also be used to study other aspects of the immunopathogenesis of HIV infection or measure serum levels of antiretroviral agents during ATI.
- **Storage:** Access to stored samples will be limited using a locked room or a locked freezer. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- **Tracking:** Samples will be tracked utilizing the repository operated by Leidos Biomedical, Inc. Data will be stored and maintained in the NIAID CRIMSON database.
- **Disposition at the Completion of the Protocol:** At the completion of the protocol (termination), samples and data will either be destroyed, or after Institutional Review Board (IRB) approval, transferred to another existing protocol.
- **Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:**
    - Any loss or unanticipated destruction of samples or data (for example, due to freezer malfunction) that meets the definition of Protocol Deviation and/or compromises the scientific integrity of the data collected for the study, will be reported to the NIH IRB.
    - Additionally, subjects may decide at any point not to have their samples stored. In this case, the PI will destroy all known remaining samples and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in this protocol or any other protocols at NIH.

10 DATA SHARING PLAN

What data will be shared?

We will share human data generated in this study for future research as follows:

- De-identified data in an NIH-funded or approved public repository.
- Identified data in the Biomedical Translational Research Information System (BTRIS).
- De-identified or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- At the time of publication or shortly thereafter.

11 REMUNERATION PLAN FOR SUBJECTS

Eligible subjects will be compensated for travel according to the NIAID/NIH travel policy. Subjects will receive financial compensation for time and inconvenience according to the NIH Clinical Center volunteer guidelines: screening ($50), leukapheresis ($200 for a 2-pass leukapheresis procedure), research blood draw ($40), clinic visits ($30), 3BNC117/10-1074 infusion ($80). If subject does not qualify or declines leukapheresis, an additional 80 mL research blood will be drawn and subject may be compensated an additional $25 for inconvenience. For participants who complete all the follow up phase visits, there is a $200 completion bonus.

12 ASSESSMENT OF SAFETY

12.1 Documenting, Recording, and Reporting Adverse Events

At designated visits with the subject, information regarding AEs will be elicited by appropriate questioning and examinations, and it will be:

- Immediately documented in the electronic database and medical record.
- Reported as outlined below (e.g., IND sponsor, IRB, Food and Drug Administration [FDA]).

12.2 Definitions

Adverse event (AE)
An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the research.

Adverse reaction (AR)
An adverse reaction (AR) is an AE that is caused by an investigational agent (drug or biologic).

Suspected adverse reaction (SAR)
A suspected AR (SAR) is an AE for which there is a reasonable possibility that the investigational agent caused the AE. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about the causality than an AR, which implies a high degree of certainty.

Serious adverse event (SAE)
An SAE is an AE that results in one or more of the following outcomes:

- Death
- A life-threatening (i.e., an immediate threat to life) event
- An inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- A medically important event*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but they may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Unexpected adverse event
An AE is unexpected if it is not listed in the IB or package insert (for marketed products), or it is not listed at the specificity or severity that has been observed. It is the responsibility of the IND sponsor to make this determination.

Serious and unexpected suspected adverse reaction
A serious and unexpected suspected AR (SUSAR) is a SAR that is both serious and unexpected.

Unanticipated problem
An unanticipated problem (UP) is an event, incident, experience, or outcome that is—

1. Unexpected in terms of nature, severity, or frequency in relation to—
    a. The research risks that are described in the IRB-approved research protocol and informed consent document; IB, or other study documents; and
    b. The characteristics of the subject population being studied; and
2. Related or possibly to participation in the research; and
3. Suggests the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized (per the IND sponsor, an AE with a serious outcome will be considered increased risk).

Unanticipated problem that is not an adverse event (UPnonAE)
An UP that is not an AE (UPnonAE) is an incident, experience, or outcome that is not associated with an AE, which meets the 3 criteria of a UP. Examples include breaches of confidentiality, accidental destruction of study records, and unaccounted-for study drug.

Protocol Deviation
Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations (PD) are designated as serious or non-serious and further characterized as:

- Those that occur because a member of the research team deviates from the protocol
- Those that are identified before they occur, but cannot be prevented
- Those that are discovered after they occur

Serious: A UP or PD is serious if it meets the definition of a Serious Adverse Event (see above) or if it compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as:

1. Serious: Non-compliance that
    a. Increases risks, or causes harm, to subjects
    b. Decreases potential benefits to subjects
    c. Compromises the integrity of the NIH-HRPP
    d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing.

12.3 Investigator Assessment of Adverse Events

If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE.

All AEs occurring from the time when the first infusion is administered through the specified study follow-up period will be documented, recorded, and reported. The PI will evaluate all AEs with respect to **Seriousness** (criteria listed above), **Severity** (intensity or grade), and **Causality** (relationship to study agent and relationship to research) according to the following guidelines.

12.3.1 Severity and Causality

The PI will grade the severity of each AE according to the Division of Aids Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, July, 2017, which can be found at https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Causality (likelihood that the event is related to the study agent) will be assessed considering the factors listed under the following categories:

Definitely related

- Reasonable temporal relationship
- Follows a known response pattern
- Clear evidence to suggest a causal relationship
- There is no alternative etiology

Probably related

- Reasonable temporal relationship

- Follows a suspected response pattern (based on similar agents)
- No evidence of a more likely alternative etiology

Possibly related
- Reasonable temporal relationship
- Little evidence for a more likely alternative etiology

Unlikely related
- Does not have a reasonable temporal relationship
  OR
- Good evidence for a more likely alternative etiology

Not related
- Does not have a temporal relationship
  OR
- Definitely due to an alternative etiology

Note:
Other factors (e.g., dechallenge, rechallenge) should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

12.4 Investigator Reporting Responsibilities to the Sponsor

12.4.1 Adverse Events

Line listings, frequency tables, and other summary AE data will be submitted to the IND sponsor per the Safety Review and Communications Plan (SRCP – see below), or as needed for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

12.4.2 Serious Adverse Events (SAEs)

SAEs (whether or not they are also UPs) must be reported on the appropriate SAE/UP report form and sent to the sponsor Clinical Safety Office (CSO) by fax or e-mail attachment. Deaths and immediately life-threatening SAEs must be reported within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness.

Sponsor clinical safety office contact information:
OCRPRO Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704

Phone 301-846-5301
Fax 301-846-6224
E-mail: rchspsafety@mail.nih.gov

12.4.3 Unanticipated Problems (UPs)

Non-serious AEs that are UPs must also be reported on the NIH Problem report form and sent to the CSO by fax or e-mail attachment no later than 7 calendar days of site awareness of the event. UPs that are not AEs are not reported to the sponsor CSO.

12.4.4 Pregnancy

Pregnancy itself is not an AE. However, complications of pregnancies are AEs and may be SAEs. Pertinent obstetrical information for all pregnancies, including pregnancies disclosed by the subject as occurring in a partner of a male subject, will be reported to the CSO via fax or e-mail within 3 business days from the site awareness of the pregnancy.

Pregnancy outcome data (e.g., delivery outcome, spontaneous or elective termination of the pregnancy) will be reported to the CSO within 3 business days of the site awareness on a protocol-specified form. In the event of pregnancy, the following steps will be taken:

- Discontinuation of the study agents
- Unblind subject (Group 1 only)
- Withdraw from the study but continue following for safety
- Report to Medical Monitor and the IRB
- Advise research subject to notify the obstetrician of study agent exposure

12.5 Investigator Reporting Responsibilities to the NIH IRB

- Assessment of Safety: AEs and other reportable events are defined in Policy 801: Reporting Research Events
- Reporting to the NIAID Clinical Director: The principal investigator will report UPs, major protocol deviations, and deaths to the NIAID Clinical Director according to institutional timelines.
- Unanticipated problems, non-compliance, and other reportable events will be reported to the NIH IRB according to Policy 801.

12.6 Follow-up of Adverse Events and Serious Adverse Events

AEs that occur following enrollment of subjects (i.e., after the first dose of bNAb or placebo) are followed until the final outcome is known or until the end of the study follow-up period.

SAEs that that are assessed by the investigator to be possibly, probably, or definitely related to study agent/placebo and that have not resolved by the end of the follow-up period will be followed until the final outcome is known. If it is not possible to obtain a final outcome for an SAE (e.g. the subject is lost to follow up), the reason a final outcome could not be obtained will be recorded by the investigator on the AE Case Report form.

SAEs that occur after study completion that are reported to and are assessed by the investigator to be possibly, probably, or definitely related must be reported to the CSO, as described above.

12.7 Sponsor's Reporting Responsibilities

SUSARs as defined in 21 Code of Federal Regulations (CFR) 312.32 and determined by the IND sponsor will be reported to the FDA and all participating investigators as IND safety reports.

The IND sponsor will also submit an IND annual report of the progress of the investigation to the FDA as defined in 21 CFR 312.33.

12.8 Halting Criteria for the Protocol

Halting the study requires immediate discontinuation of the study agents administered for all subjects and suspension of enrollment until a decision is made about whether or not to continue study agent administration.

The halting criteria (as determined by the study PI and IND sponsor secondary to aggregate data review) for this study include:

- Any SAE or grade 4 AE that is possibly, probably, definitely related to the study agent; OR
- Any safety issue that the study PI or IND sponsor determines should halt the study.

Any related AE that is ≥ grade 3 (not including transient, subjective infusion-related symptoms such as malaise, fatigue, headache, chills) will be reviewed within 48 hours of site awareness, by the PI and IND sponsor medical monitor, to consider the need for halting the protocol.

The PI and/or CSO will determine if the study should be halted. In addition, the FDA or DSMB may halt the study at any time following review of any safety concerns.

12.8.1 Reporting of Study Halting

If a halting rule is met, a description of the AE(s) or safety issue must be reported by the PI, within one business day, to the CSO and to the IRB by fax or email. The sponsor will notify the FDA as soon as possible that the study has been halted.

12.8.2 Resumption of a Halted Study

The IND Sponsor, in collaboration with the PI will determine if it is safe to resume the study. The PI will notify the IRB and DSMB of the decision on resumption of the study. The sponsor will notify the FDA as soon as possible that the study has been resumed after a halt.

12.9 Pausing Criteria for a Subject

The decision to suspend administration of the study agent for a single subject requires discontinuation of the study agent administrated for the study subject until a decision is made whether or not to continue study agent administration.

The pausing criteria for a single subject in this study include:

- A subject experiences an SAE or grade 3 or greater AE (not including transient, subjective infusion-related symptoms such as malaise, fatigue, headache, chills, or total bilirubin in subjects taking atazanavir) that is (as determined by the IND sponsor) possibly, probably, or definitely related to the study agent;

OR

- A subject experiences a grade 2 or higher ophthalmic AE, judged to be at least possibly related to 3BNC117 and/or 10-1074, or any grade 3 or 4 ophthalmic AE, regardless of causality assessment. Additional dosing for the subject will be halted pending review and recommendation by the study clinical safety officer**.**

OR

- Any safety issue that the PI determines should pause administration of the study agent to a single subject.

The CSO, in collaboration with the PI, may also pause for an individual subject or the entire group if a safety concern is identified during routine aggregate data analysis.

12.9.1 Reporting of Pause

If a pausing requirement is met, a description of the AE(s) or safety issue must be reported by the PI by fax or e-mail within 1 business day to the sponsor CSO, PI, IRB, and the Medical Monitor. The sponsor will notify the FDA as soon as possible that the study agent has been halted for an individual subject.

12.9.2 Resumption of Pausing for a Subject or Group

The CSO in collaboration with the PI will determine whether or not it is safe to resume administration of the study agent to the subject. The PI will notify the IRB of the decision to resume administration of the study agent prior to resumption. The sponsor will notify the FDA and DSMB as soon as possible that the study agent has been resumed for an individual subject.

A subject who does not resume study agent will continue to be followed for safety.

12.10 Withdrawal Criteria for an Individual Subject

An individual subject will be withdrawn for any of the following:

- An individual subject's decision. (The PI will attempt to determine the reason for the subject's decision and will strongly suggest a follow-up plan to help ensure the subject safely returns to baseline or better, if possible).
- Co-enrollment in a study with an investigational research agent (rare exception granted by the PI).
- Any SAE or grade 4 systemic infusion related symptom(s) or AE that is considered to be related to the study agent.
- Clinically significant type 1 hypersensitivity reaction associated with the study agent. In the event of a type 1 hypersensitivity reaction that is NOT considered to be clinically significant, (e.g., brief, mild, and self-limited skin reaction without other

symptoms), the PI may consider possible additional infusions of the study agent with appropriate precautions.
- Any clinical AE, laboratory abnormality, or other medical condition or situation such that continued participation in the study would not be in the best interest of the subject. Subjects will be followed for the duration of the study for indicated safety assessments.
- Non-compliance with study procedures to the extent that it is potentially harmful to the subject or to the integrity of the study data.
- Pregnancy.
- Subject misses more than 2 study infusions.

If possible, all subjects who discontinue the study treatment prematurely will be followed for 6 months for all the study evaluations.

12.11 Replacement for Withdrawn Subjects

Any subject who withdraws from the study, or who discontinues the study agent, prematurely, and whose reasons for withdrawing from the study or discontinuing study agent administration are unrelated to any real or perceived effect of the study agent or their administration, may be replaced at the discretion of the PI.

12.12 Safety Oversight

12.12.1 Safety Review and Communications Plan (SRCP)

A Safety Review and Communications Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the PI and the IND sponsor CSO, which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

12.12.2 Sponsor Medical Monitor

A medical monitor, representing the IND sponsor (OCRPRO), has been appointed for the safety oversight in this clinical study. The sponsor medical monitor will be responsible for performing safety assessments as outlined in the SRCP.

12.13 Data Safety Monitoring Board (DSMB)

The NIAID Intramural DSMB includes independent experts that do not have direct involvement in the conduct of the study and have no significant conflicts of interests as defined by NIAID policy. The Board will review the study prior to initiation and twice a year thereafter. An alternative schedule may be indicated (i.e., interim analysis)]**.** The Board may convene additional reviews as necessary. The Board will review the study data to evaluate the safety, efficacy, study progress, and conduct of the study. All SAEs, all UPs, and all IND Safety Reports will be reported by the PI to the DSMB at the same time they are submitted to the IRB or IND Sponsor. The PI will notify the DSMB of any cases of intentional or unintentional unblinding as

soon as possible. The PI will notify the Board at the time pausing or halting criteria are met and obtain a recommendation concerning continuation, modification, or termination of the study. The PI will submit the written DSMB summary reports with recommendations to the IRB(s).

13 CLINICAL MONITORING STRUCTURE

SITE MONITORING PLAN

As per ICH-GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. This study monitoring will be conducted according to the *"NIAID Intramural Clinical Monitoring Guidelines."* Monitors under contract to the NIAID/ OCRPRO will visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the informed consent form (ICF) process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare CRIMSON data abstracts with individual subjects' records and source documents (subjects' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections [OHRP], FDA), and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (e.g., consent forms, CRIMSON data abstracts, and pertinent hospital or clinical records readily available for inspection by the local IRB, the FDA, the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the PI and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status and regulatory obligations.

13.1 Study Blinding and Unblinding (Group 1)

Study subjects and site staff (except for the NIH pharmacists) will be blinded to the subject treatment arm assignments (e.g., active treatment or control). Any discussion about the study product assignment between the pharmacy staff and any other protocol staff is prohibited. The Data and Safety Monitoring Board (DSMB) members also are unblinded to the treatment assignment for the review of trial safety.

When a subject leaves the trial prior to study completion, the subject will be told he or she must wait until the all the subjects are unblinded to learn about his or her treatment assignment.

Emergency unblinding decisions will be made by the PI. If time permits, the sponsor medical monitor will be consulted before emergency unblinding occurs.

14 STATISTICAL CONSIDERATIONS

The primary safety outcome is the occurrence of grade 3 or higher AEs. An exact 95% confidence interval for the probability of AEs will be computed using the Clopper-Pearson method. The primary efficacy outcome is rebound of plasma viremia requiring a restart of ART. An exact 95% confidence interval will be computed for the rebound probability using the Clopper-Pearson method. Changes from baseline in continuous measurements will be analyzed using paired t-tests or, if data are skewed, the Wilcoxon signed rank statistic.

In terms of safety, a sample size of 30 subjects provides a 95.8% chance of observing an AE of probability 10% or greater. Table 1shows the chance of observing at least one AE of given probability.

Table 1. Chance of AE of Given Probability

	Probability					
Row 1	0.025	0.050	0.075	0.100	0.125	0.150
Row 2	0.532	0.785	0.904	0.958	0.982	0.992

The second row is the probability of observing at least one AE of probability given in the first row for the 30 subjects receiving 3BNC117 plus 10-1074.

Group 1 Efficacy Endpoint

Sample size justification is based on data from a recently completed NIAID therapeutic vaccine study of early treated subjects (Protocol 13-I-0141)[28]. In the Placebo arm of the therapeutic vaccine study, 80% of subjects would have met the criteria listed in Section 3.1 to restart ART prior to study week 32. Table 2 shows power for ART restart probabilities between 0.20 and 0.30 in the 3BNC117 plus 10-1074 arm. Power is approximately 87% and 80% for ART restart probabilities of 0.20 and 0.24 in the 3BNC117 plus 10-1074 arm.

Table 2. Power shown in row 2 for different ART restart probabilities in the 3BNC117 plus 10-1074 arm (row 1). The restart probability in the placebo arm is assumed to be 0.80.

Restart Prob. bNAb arm	0.20	0.22	0.24	0.26	0.28	0.30
Power	0.872	0.840	0.804	0.765	0.724	0.680

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an on-going conversation between the human research subject and the researchers which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, experimental procedures, alternatives, risks and benefits. Subjects will be given the opportunity to ask questions and have them answered.

The subjects will sign the informed consent document prior to undergoing any research procedures. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The researcher will document the signing of the consent form in the subject's medical record. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

15.1.1 Non-English–Speaking Subjects

If a non-English-speaking subject is eligible for enrollment, the subject will be provided with the CC Short Written Consent Form for Non-English-speaking Research Participants in the subject's native language and a verbal explanation of the purpose, procedures and risks of the study as described in MAS Policy M77-2, NIH HRPP SOP 12 and 45 CFR 46.117(b)(2). The IRB-approved English consent form will serve as basis for the verbal explanation of the study. The investigator will obtain an interpreter unless the investigator is fluent in the prospective subject's language. Preferably, the interpreter will be someone who is independent of the subject (i.e., not a family member). Interpreters provided by the CC will be used whenever possible. The interpreters will translate the IRB-approved English consent form verbatim and facilitate discussion between the subject and investigator.

The IRB-approved English consent form will be signed by the investigator obtaining consent and a witness to the oral presentation. The CC Short Written Consent Form will be signed by the subject and a witness who observed the presentation of information. The interpreter may sign the consent document as the witness and, in this case, will note "Interpreter" under the signature line. A copy of both signed forms will be provided to the subject to take home.

The investigator obtaining consent will document the consent process in the subject's medical record (CRIMSON), including the name of the interpreter. Further, all instances of use of the CC Short Written Consent Form will be reported to the IRB at the time of annual review. If the CC Short Written Consent Form is used three times or more for the same language, this will be reported to the IRB immediately.

<u>Illiterate English Speaking Subjects</u>
As the majority of the subject populations from which the study subjects are drawn are literate, written consent will typically be provided. However, this population does have a small rate of illiteracy, and oral consent will be obtained for illiterate subjects as consistent with NIH MAS Policy M77-2 without separate IRB approval for each specific use. At Continuing Reviews, the NIH IRB will be informed of the number of illiterate subjects who provided consent verbally.

15.2 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, NIAID, OHRP, or the sponsor's designee.

16 DATA HANDLING AND RECORD KEEPING

16.1 Data Capture and Management

Study data will be maintained in CRIMSON and collected directly from subjects during study visits and telephone calls, or will be abstracted from subjects' medical records. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary to confirm the data abstracted for this study. Data entry into CRIMSON will be performed by authorized individuals. Corrections to CRIMSON shall be tracked electronically with time, date, individual making the correction, and what was changed.

The investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

16.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the International Conference for Harmonization Good Clinical Practice Guidelines. Study records will be maintained by the PI for a minimum of 3 years and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law. The FDA requires study records to be retained for up to two years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator will provide written notification of such intent to OCRPRO/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. Destruction or relocation of research records will not proceed without written permission from NIAID/OCRPRO.

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APPENDIX A: AE REPORTED UNDER PROTOCOLS MCA-0906 AND YCO-0899

(YCO-0899 remains blinded)

Adverse Events	No. AEs	No. Mild	No. Moderate	No. Severe	No. of participants
Related to 3BNC117 and 10-1074 Infusions					
Malaise/Fatigue	2	2	0	0	2
Upper respiratory infection	2	2	0	0	2
Elevated bilirubin	1	1	0	0	1
Headache	1	1	0	0	1
Hyperthermia	1	0	0	1	1
Nausea	1	1	0	0	1
Transaminitis	1	1	0	0	1
Total related	**9**	**8**	**0**	**1**	**9**
Not Related to 3BNC117 and 10-1074 Infusions					
Upper respiratory infection	9	9	0	0	9
Headache	4	4	0	0	3
Urethritis (gonorrhea, or mycoplasma)	3	1	2	0	2
Anemia	2	2	0	0	1
Elevated bilirubin	2	2	0	0	2
Intermittent increase in direct bilirubin*	2	0	0	2	2
Sore throat	2	1	0	0	1
Vomiting	2	1	1	0	2
Abdominal distension	1	0	0	0	1
Agitation	1	1	0	0	1
Albuminuria	1	1	0	0	1
Altered mental status (drug-intoxication related)	1	0	0	1	1
Epistaxis	1	1	0	0	1
Hypoglycemia	1	1	0	0	1
Increased tearing of left eye	1	1	0	0	1
Malaise/Fatigue	1	0	0	0	1
Myalgia	1	0	0	0	1
Nausea	1	1	0	0	1
Shoulder pain	1	1	0	0	1
Stye	1	1	0	0	1
Urinary retention	1	0	0	0	1
Total Not related	**39**	**28**	**3**	**3**	**35**
Total AE's	**48**	**36**	**3**	**4**	**44**

* Direct bilirubin level was 0.3 mg/dL (normal range 0-0.29 mg/dL). Level was considered grade 3 according to the DAIDS Toxicity Table, version 2.0.

APPENDIX B: STUDY FLOW SHEET

Group 1 and 2

Study Point		Screening
Date Range		UP TO 8 wks Before Enrollment
PROCEDURES / CONSULTS		
Consent		X
ECG	12 LEAD	X
DTM Apheresis Assessment		X
Medical History, Targeted PE, Sympton Directed Eval, VS, Wgt, Medication Review		X
Ophthalmologic Exam (within 8 weeks prior to first study infusion)		X
LABS:		
Pregnancy (Blood or Urine)		X
CBC with Diff		X
PT, aPTT		X
Creatinine, Total and Direct Bili, Serum Albumin		X
HBsAG,		X
Anti-HCV Antibody & HCV RNA Quant		X
Urinalysis		X
RESEARCH LABS:		
(WHBL) Flow Cytometry with CD4+		X
(Abbott HIV RTPCR) HIV Viral Load		X
Plasma Storage		X
Serum Storage		X
PBMC Storage		X
Blood volume will not exceed current NIH limits as defined by MAS-95-9.		

Appendix B continued:
Group 1 Infusion / ATI Phase

Study Point		NNRTI SWITCH	Pre-Tx Apheresis #1	Baseline	ART STOP	Infusion 2	Infusion 3	Blood Draw	Infusion 4	Blood Draw	Infusion 5	Blood Draw		Apheresis #2	Infusion 6	Blood Draw	Infusion 7	Blood Draw	Infusion 8	Apheresis #3	Extended ATI Phase
Date Range		> 2 WKS BEFORE DAY ZERO	Post Screen & Pre FIRST INFUSION	Day Zero	DAY 4	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14		Wk 16 (Before Infusion)	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	+/- 14 days after Wk 24	If pt has not met Group 1 ATI Restart Criteria by week 24, Continue to Extended ATI Phase Flowsheet.
Protocol Visit Date																					
PROVIDERS:																					
CM Visit				X	Telephone note	X	X		X		X				X		X		X		
LIP Visit				X		X	X		X		X				X		X		X		
PROCEDURES / CONSULTS:																					
Pts on NNRTIs switch to Protease or Integrase inhib		X																			
Medical History, Targeted PE, Sympton Directed Eval, VS, Wgt, Medication Review				X		X	X		X		X				X		X		X		
Assess AEs / Intercurrent illnesses				X		X	X		X		X				X		X		X		
APHERESIS	2L		**X**										2L	**X**						**X**	
HIV Transmission Risk Assessment / Counsel				X		X	X		X		X				X		X		X		
Infusion: (3BNC117 & 10-1074) or Placebo				X		X	X		X		X				X		X		X		
LABS:																					
CBC with Diff				X		X	X		X		X				X		X		X		
Chem: ALT, AST, AlK Phos, Creatinine, Total and Direct Bili, Serum Albumin				X		X	X		X		X				X		X		X		
Pregnancy (POC)- Result must be Neg Before Infusion	Urine			X		X	X		X		X		Urine		X		X		X		
HLA (IF not already done at NIH)				X																	
RESEARCH LABS:																					
(WHBL) Flow Cytometry with CD4+				X		X	X	X	X	X	X	X			X	X	X	X	X		
(Abbott HIV RTPCR) HIV Viral Load				X		X	X	X	X	X	X	X			X	X	X	X	X		
HIV Genotype >1000 VL						X	X	X	X	X	X	X			X	X	X	X	X		
Plasma Storage				X		X	X	X	X	X	X	X			X	X	X	X	X		
Serum Storage				X		X	X	X	X	X	X	X			X	X	X	X	X		
(PBL Storage) PBMC Storage				X		X	X	X	X	X	X	X			X	X	X	X	X		
ONLY If PT Cannot apherese	30 mL Hep Syringe		X										30 mL Hep Syringe	X						X	
ONLY If PT Cannot apherese	50 mL Hep Syringe		X										50 mL Hep Syringe	X						X	
Blood volume will not exceed current NIH limits as defined by MAS-95-9.																					

Appendix B continued:

Group 1 Extended ATI Phase

Study Point		Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	Wk 36	Wk 38	Wk 40	Wk 42	Wk 44	Wk 46	Wk 48	Wk 50		Wk 52	Wk 54	Wk 56	Wk 58	Wk 60	Wk 62	Wk 64	If VL>40, but <1000 at Wk 64, will be advised to restart ART and will move to the Follow up Phase	If VL <40 at week 64, may remain off ART and have CD4 and VL drawn every 4 weeks till viremia is dectected.
PROCEDURES / CONSULTS:																								
Physical Exam			x		x		x		x		x		x			x		x		x		x		
LABS:																								
CBC			x		x		x		x		x		x			x		x		x		x		
RESEARCH LABS:																								
(WHBL) Flow Cytometry with CD4+		x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x		x
(Abbott HIV RTPCR) HIV Viral Load		x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x		x
Plasma Storage		x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x		x
Serum Storage		x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x		x
PBMC Storage		x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x		x
Blood volume will not exceed current NIH limits as defined by MAS-95-9.																								

Appendix B continued:

Group 2 Infusion Phase

Study Point		Pre-Tx Apheresis #1	Baseline	Infusion 2	Infusion 3	Blood Draw	Infusion 4	Blood Draw	Infusion 5	Blood Draw	Apheresis #2	Infusion 6		Blood Draw	Infusion 7	Blood Draw	Infusion 8	Apheresis #3	
Date Range		Post Screen & Pre Enrollment INFUSION	Day Zero	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16 (Before Infusion)	Wk 16		Wk 18	Wk 20	Wk 22	Wk 24	+/- 14 days after Wk 24	Move to Follow Up Phase after Wk 24
Protocol Visit Date																			
PROCEDURES / CONSULTS:																			
Medical History, Targeted PE, Sympton Directed Eval, VS, Wgt, Medication Review			X	X	X		X		X			X			X		X		
Assess AEs / Intercurrent illnesses			X	X	X		X		X			X			X		X		
APHERESIS	2L	**X**									**X**		2L					**X**	
HIV Transmission Risk Assessment / Counsel			X	X	X		X		X			X			X		X		
Infusion: 3BNC117 & 10-1074			X	X	X		X		X			X			X		X		
LABS:																			
Pregnancy (POC)- Result must be Neg Before Infusion	Urine		X	X	X		X		X			X	Urine		X		X		
CBC with Diff			X	X	X		X		X			X			X		X		
Chem: ALT, AST, AlK Phos, Creatinine, Total and Direct Bili, Serum Albumin			X	X	X		X		X			X			X		X		
HLA (IF not already done at NIH)			X																
RESEARCH LABS:																			
(WHBL) Flow Cytometry with CD4+			X	X	X	X	X	X	X	X		X		X	X	X	X		
(Abbott HIV RTPCR) HIV Viral Load			X	X	X	X	X	X	X	X		X		X	X	X	X		
HIV Genotype >1000 VL	Same Tube as VL			X	X	X	X	X	X	X		X	Same Tube as VL	X	X	X	X		
Plasma Storage			X	X	X	X	X	X	X	X		X		X	X	X	X		
Serum Storage			X	X	X	X	X	X	X	X		X		X	X	X	X		
(PBL Storage) PBMC Storage			X	X	X	X	X	X	X	X		X		X	X	X	X		
ONLY If PT Cannot apherese	30 mL Hep Syringe	X									X		30 mL Hep Syringe					X	
ONLY If PT Cannot apherese	50 mL Hep Syringe	X									X		50 mL Hep Syringe					X	
Blood volume will not exceed current NIH limits as defined by MAS-95-9.																			

Appendix B continued: Group 1 Follow Up Phase

Study Point		F/U Wk 4	F/U Wk 12	F/U Wk 24
Protocol Visit Date				
PROCEDURES / CONSULTS				
Apheresis	2L			**X**
NIH Visit		X	X	X
Medical History, Targeted PE, Sympton Directed Eval, VS, Wgt, Medication Review		X	X	X
Assess AEs / Intercurrent illnesses		X	X	X
LABS:				
Pregnancy (POC)- Result must be Neg Before Apheresis				X
CBC with Diff		X	X	X
Chem: ALT, AST, AlK Phos, Creatinine, Total and Direct Bili, Serum Albumin		X	X	X
RESEARCH LABS:				
(WHBL) Flow Cytometry with CD4+		X	X	X
(Abbott HIV RTPCR) HIV Viral Load		X	X	X
HIV Genotype (Group One: If VL >1000)		X	X	X
Plasma Storage		X	X	X
Serum Storage		X	X	X
PBMC Storage		X	X	X
ONLY If PT Cannot apherese	30 mL Hep Syringe			X
ONLY If PT Cannot apherese	50 mL Hep Syringe			X
Blood volume will not exceed current NIH limits as defined by MAS-95-9.				

Appendix B continued: Group 2 Follow-Up Phase

Study Point		Optional F/U Week 2	F/U Wk 4	Optional F/U Week 6	Optional F/U Week 8	Optional F/U Week 10	F/U Wk 12	Optional F/U Week 16	Optional F/U Week 20	F/U Wk 24
Protocol Visit Date										
PROCEDURES / CONSULTS										
Apheresis										**X**
NIH Visit			X				X			X
Med History, PE (Focused SXS exam), VS, Wgt, Medication Review			X				X			X
Assess AEs / Intercurrent illnesses			X				X			X
LABS:										
Pregnancy (POC)- Result must be Neg Before Apheresis										X
CBC with Diff			x				x			x
Acute Care/Hepatic/Mineral Panel			x				x			x
RESEARCH LABS:										
(WHBL) Flow Cytometry with CD4+		x	x	x	x	x	x	x	x	x
(Abbott HIV RTPCR) HIV Viral Load		x	x	x	x	x	x	x	x	x
HIV Genotype (Group One: If VL >1000)			X				X			X
Plasma Storage		x	X	x	x	x	X	x	x	X
Serum Storage		x	X	X	X	x	x	x	x	x
PBMC Storage		x	X	X	X	X	X	X	X	X
ONLY If PT Cannot apherese	30 mL Hep Syringe									X
ONLY If PT Cannot apherese	50 mL Hep Syringe									X
Special Tubes										
Vists May Be Offsite										
Blood volume will not exceed current NIH limits as defined by MAS-95-9.										