Effect of Infusion of Broadly Neutralizing Antibody VRC01 on HIV Plasma Rebound

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Abstract

Background: Recent advances in immunogen and antibody cloning technologies have led to the isolation of several highly potent and broadly neutralizing HIV-specific antibodies (bNAb) from B cells of infected individuals[1-3]. VRC01 has proven to be effective in neutralizing diverse strains of HIV in vitro and in animal models and has the capacity to suppress plasma viremia in infected individuals[4]. However, the ability of VRC01 to suppress plasma viral rebound in HIV-infected patients following cessation of antiretroviral therapy (ART) remains unclear.

Methods: An exploratory, open-label clinical trial was conducted to examine the effect of passive transfer of VRC01 on plasma viral rebound following discontinuation of ART in HIV-infected individuals who initiated treatment during the chronic phase of infection and who suppressed plasma viremia >3 years with CD4+ T cell count > 450 cells/mm^3 at enrollment. Subjects received VRC01 (40mg/kg) 3 days prior to and 14 and 28 days following interruption of ART, and monthly thereafter for up to 6 months. Levels of plasma viremia and VRC01 were measured at day -7, -3, 0, 3, 7, 14, 21, and 28 and biweekly thereafter. In addition, the capacity of VRC01 and other bNAbs to neutralize autologous infectious HIV prior to and following infusions of the antibody was examined.

Results: Ten subjects were enrolled in the study. Mean duration of ART was 10.6 years. Mean CD4+ and CD8+ T cell counts at baseline were 796 and 768/mm^3, respectively. Multiple infusions of VRC01 were safe and well tolerated. Ten of ten subjects experienced plasma viral rebound (>40 copies/ml) between 11-86 days (median 39) following cessation of ART; 9 subjects reinitiated ART per protocol. Plasma concentration of VRC01 ranged between 142-583 μg/ml (median 169) at time of first detectable plasma viremia. Preliminary analyses of autologous replication-competent viral isolates revealed the existence of VRC01-resistent virus prior to infusion of antibody in several subjects. Additionally, emergence of VRC01-resistant infectious HIV was detected in the study participants at the time of plasma viral rebound.

Conclusions: While multiple infusions of VRC01 were safe and well-tolerated, the majority of patients experienced plasma viral rebound despite adequate levels of antibody in plasma. Therefore, therapeutic strategies involving passive transfer of bNAbs may require a combination of Abs and/or resistance prescreening in order to achieve sustained virologic control in HIV-infected individuals upon withdrawal of ART.

Background and Rationale

- Plasma viremia rapidly rebounds in virtually all HIV-infected individuals upon cessation of therapy[5]
- The burden of taking daily medication necessitates a continued search for effective treatment alternatives
- HIV-specific bNAbs can neutralize emerging HIV, block cell-to-cell spread of HIV, and facilitate the clearance of plasma virus and HIV-infected cells[6-10]
- This study evaluates the safety and tolerability of multiple doses of VRC01 as well as the effect on viral rebound following discontinuation of ART

Materials and Methods

Study Population: HIV-infected individuals who initiated ART during the chronic phase of infection (Table 1).
Study Design: A single-arm, open-label study was designed to examine the effect of VRC01 on plasma viral rebound in HIV-infected individuals following an analytical treatment interruption (ATI).
Study Agent: VRC01 is a recombinant human IgG1 directed against the CD4-binding site of HIV gp120.
Viremia Quantification: Plasma viremia was evaluated biweekly with the limitation of detection of 40 HIV RNA copies/mL.
Pharmacokinetic analyses: Measurements of VRC01 plasma concentration were performed using the anti-idiotype mAb 5C9.
HIV neutralization: Multiple infectious HIV isolates were obtained from stimulated PBMCs prior to and following infusions of VRC01. The viral isolates were pre-incubated with human IgG, VRC01, 3BNC117, 10-1074, or PGT121 (10μg/ml) for 90 minutes and added to TZM-bl cells. Following a 2 day incubation period, cells were lysed and the viral infectivity was quantitated by measuring luciferase activity.
Treatment Phase: VRC01 was administered on day 0 and ART discontinued on day 3. Subsequent infusions of VRC01 occurred at week 2, 4, and every 4 weeks thereafter until week 24 for a total of 8 doses.
Reinitiation of ART: The subject was instructed to restart ART if any of the following criteria were met: 1) >30% decline in baseline CD4 cell count, 2) absolute CD4 cell count <350 cells/mm3, 3) a sustained (≥4 weeks) HIV RNA level of >1,000 copies/mL, 4) any HIV-related symptoms, or 5) pregnancy.

Results

Figure 1

Plasma viremia in study participants following discontinuation of ART

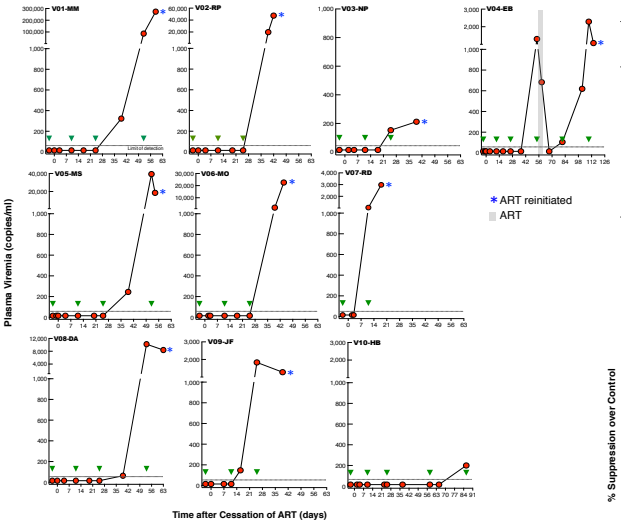


Figure 2

Levels of plasma viremia and VRC01 in study participants

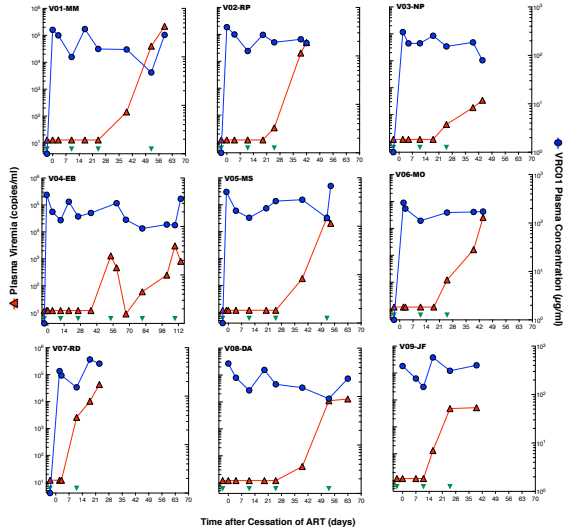


Table 1

Demographic and immunologic profiles of HIV-infected Individuals

Subject	Duration of ART* (years)	CD4+ T cell count at baseline	CD4+ T cell % at baseline	CD8+ T cell count at baseline	CD8+ T cell % at baseline	Plasma viremia at the time of study
V01-MM	13.8	1,166	49	762	32	<40
V02-RP	17.2	728	47	526	34	<50
V03-NP	9.2	1,194	47	813	32	<40
V04-EB	11.8	726	50	581	40	<40
V05-MS	14.2	577	38	577	38	<40
V06-MO	7.3	594	32	873	47	<40
V07-RD	7.7	722	29	623	25	<40
V08-DA	6.9	634	50	406	32	<40
V09-JF	7.8	992	34	1,372	47	<40
V10-HB	10.7	628	30	1,151	55	<40

Figure 3

Time to plasma viral rebound in study participants

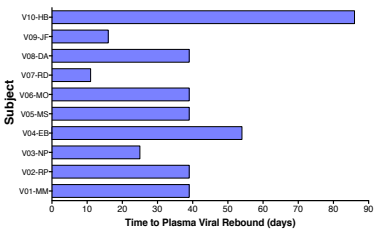
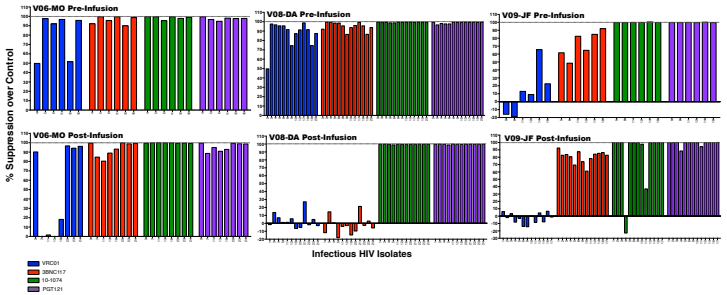


Figure 4

Capacity of bNAbs to neutralize autologous replication competent HIV prior to and following infusions of VRC01



Conclusions

- Multiple infusions of VRC01 were safe and well-tolerated.
- The majority of patients experienced plasma viral rebound following discontinuation of HAART despite adequate plasma levels of antibody.
- Pre-existing and rapid emergence of VRC01-resistant HIV likely contributed to plasma viral rebound.
- Therapeutic strategies involving passive transfer of bNAbs may require a combination (s) of Abs and/or resistance prescreening in order to achieve sustained virologic control in HIV-infected individuals upon withdrawal of ART.

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