# Neutralizing Antibody, VRC01, PK and Safety Among Infants Initiating Very Early ART in IMPAACT P1115

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## BACKGROUND

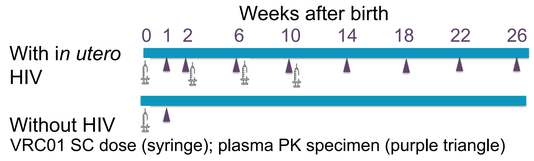
Very early antiretroviral treatment (ART) resulting in effective viral suppression can enable ART-free remission for infants with *in utero* HIV-1.[1] However, many infants do not achieve sustained viral suppression. Anti-HIV-1 broadly neutralizing antibodies (bNAbs) show promise as long-acting agents for treatment of HIV-1 and may contribute to remission.[2] However, safety and pharmacokinetic (PK) data for bNAbs given to infants with HIV-1 are limited.

We studied the safety and PK of VRC01, an anti-CD4 binding site bNAb, administered at birth with the initiation of very early ART for infants at risk of *in utero* HIV-1 acquisition.

## METHODS

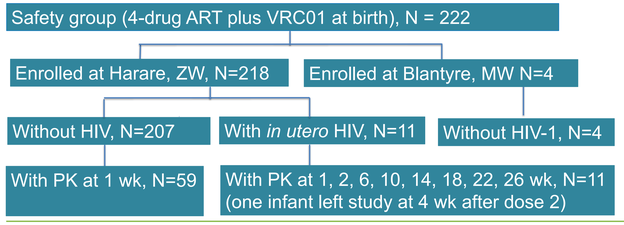
All infants enrolled at two IMPAACT P1115 sites in Zimbabwe and Malawi initiated 4-drug ART (raltegravir, nevirapine, 2 NRTI) within 48 hours (hr) of birth and received 40 mg/kg VRC01 by slow subcutaneous (SC) push (~10 minutes) within 72 hr of birth. Infants with confirmed *in utero* HIV-1 received 3 additional 40mg/kg VRC01 doses at 2, 6, and 10 weeks (wk) of age. Reactogenicity and safety were assessed in all infants. Plasma VRC01 concentrations were assessed in a subgroup of infants without confirmed *in utero* HIV-1 (Without HIV) enrolled early (study years 1 and 2) and in all infants with *in utero* HIV-1 (With *in utero* HIV). Observed VRC01 concentrations, categorized by concurrent HIV-1 RNA values, and predicted VRC01 concentrations from modeling of IMPAACT P1112 data[3] for infants HIV-1 exposed but uninfected (HEU) were visualized. VRC01 concentrations below the limit of quantitation (BQL) were assumed equal to 0.5 mcg/mL when calculating quantiles.

**FIGURE 1. VRC01 dosing and plasma PK sampling.**




VRC01 SC dose (syringe); plasma PK specimen (purple triangle)

**FIGURE 2. Consort diagram.**




**VRC01 was safe and well tolerated when given SC at birth. Concentrations after the first dose in the first week of life were similar for infants with and without HIV but clearance was faster among infants with HIV than predicted from studies of infants exposed but without HIV.**

## RESULTS

**TABLE 1. Infant baseline characteristics.**

| | PK | No PK | All |
|---|---|---|---|
| **Characteristic** | **N=70** | **N=152** | **N=222** |
| Sex % male | 44.3% | 53.3% | 50.5% |
| Gestational age (wk) median (Q1-Q3) | 38 (38-40) | 38 (37-40) | 38 (37-40) |
| Birth weight (kg) mean (± SD) | 2.8 (0.4) | 2.8 (0.4) | 2.8 (0.4) |
| Age (hr) at 1st ART median (Q1-Q3) | 23.2 (16.3-28.0) | 13.7 (6.4-25.0) | 17.6 (8.2-26.2) |

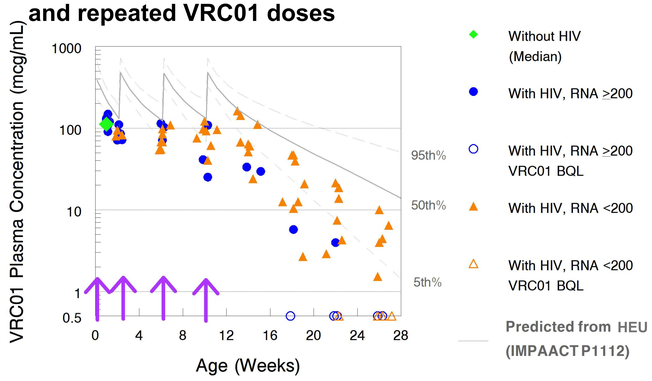
**TABLE 2. Local and systemic reactogenicity.**

| | | # with reaction | | | |
|---|---|---|---|---|---|
| | | Dose Number receiving dose | | | |
| **Infant group** | **Reaction Type** | **1 N=222** | **2 N=11** | **3 N=10** | **4 N=10** |
| Without HIV | Local | 3 | NA | NA | NA |
| | Systemic | 0 | NA | NA | NA |
| With *in utero* HIV | Local | 0 | 0 | 0 | 0 |
| | Systemic | 0 | 0 | 0 | 0 |

| | Local reaction | |
|---|---|---|
| **Infants with local reactions¥** | **Edema** | **Tenderness** |
| # infants | 2 | 1 |
| Maximum grade | 1 | 1* |
| Maximum diameter (cm) range | 1-3 | NA |
| Duration (minutes) range | 22-45 | 45 |

¥All infants with local reaction were enrolled in Blantyre
*Mild pain with touch, minimal limitation of movement of limb

**FIGURE 3. Plasma VRC01 concentrations after birth and repeated VRC01 doses**




VRC01 concentrations 1 wk after the birth dose for Without HIV and With HIV, and after repeated doses for With HIV compared to median and 95% confidence intervals for modeled data from HEU infants enrolled in IMPAACT P1112. Concentrations for With HIV are categorized by concurrent HIV-1 RNA values (copies/ml). Purple arrows indicate VRC01 doses. BQL = below the limit of quantitation, set to 0.5 mcg/mL.

**TABLE 3. VRC01 plasma concentrations.**

| | VRC01 concentration (mcg/mL) Median [25th -75th percentile] (# tested) | |
|---|---|---|
| **Age** | **Without HIV-1** | **With *in utero* HIV-1** |
| 1 wk* | 110.2 [95.2, 131.0] (n=59) | 118.4 [108.8, 126.9] (n=10)^ |
| 2 wk¥ | NA | 82.6 [71.9, 87.6] (n=11) |
| 6 wk£ | NA | 77.8 [67.8, 102.6] (n=10) |
| 10 wk£ | NA | 84.0 [41.2, 97.6] (n=10) |
| 14 wk£ | NA | 62.4 [33.4, 111.0] (n=10) |

^One infant lacked a specimen at 1 wk. *One wk after birth dose; ¥Two wk after birth dose; £Four wk after doses given at 2, 6, and 10 wk of age.

**TABLE 4. Post-baseline Grade 3 or higher adverse events within 37 days of birth (n=222)**

| | Related * | | All | | |
|---|---|---|---|---|---|
| | **Grade 3** | **Grade 4** | **Grade 3** | **Grade 4** | **Grade 5** |
| Overall | 2 (1%) | 2 (1%) | 8 (4%) | 3 (1%) | 1 (0%) |
| Neutrophil count decreased | 2 | 2 | 4 | 3 | 0 |
| Platelet count decreased | 0 | 0 | 1 | 0 | 0 |
| Bilirubin increased | 0 | 0 | 2 | 0 | 0 |
| Dyspnoea | 0 | 0 | 1 | 0 | |
| Serious bacterial infection | 0 | 0 | 2 | 0 | 1 |

*Related events were attributed to ART regimen.

## CONCLUSIONS

- No safety concerns and very rare local injection reactions were identified in over 200 newborns who received VRC01 SC at birth concurrent with initiation of ART.
- VRC01 was rapidly absorbed after SC administration.
- VRC01 plasma concentrations were similar among infants with and without *in utero* HIV at one week after the first dose; infants with *in utero* HIV, particularly those with ongoing viremia, had more rapid clearance than predicted from data in HEU, perhaps due to target-mediated drug deposition.
- HIV-1 status and viremia should be considered in bNAb dosing strategies for infants initiating ART.

**Plain Language Summary**
Antibodies against HIV might help to treat infants living with HIV. An antibody called VRC01, given to infants in the days and weeks after birth, was safe and rapidly absorbed. Tthe amount of antibody in the blood of infants with HIV dropped faster than in infants without HIV. This suggests that higher doses of antibodies will be needed for treatment of infants with HIV.

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