Supplementary Appendix

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Supplementary Appendix 1: Protocol on the management of infusion reactions

Cutaneous involvement (eg, urticaria or hives; localized or generalized) without airway angioedema	**Systemic Anaphylaxis-like reactions (eg, with airway angioedema or other respiratory or cardiovascular compromise)**
1. **STOP** infusion immediately	**1.** **STOP** infusion immediately
2. **Change IV tubing** (maintaining access if possible) to administer **normal saline**	**2.** **Change IV tubing** (maintaining access if possible) to administer **normal saline**
3. Obtain **vital signs** and complete a focused **physical exam**	**3.** Obtain **vital signs** and complete a focused **physical exam**
4. (Not Applicable)	**4.** Administer **epinephrine / adrenaline IM & repeat PRN**
5. Administer **antihistamine PO, IM, or IV** (choice to administer, route of administration, and dose is determined by investigator judgment based on severity of symptoms and access) Cetirizine 10mg PO[1] OR Promethazine 25mg PO, IM, or IV[2] OR Diphenhydramine 50mg PO, IM, or IV[3]	**5.** Administer **antihistamine IM or IV** (choice to administer, route of administration, and dose is determined by investigator judgment based on severity of symptoms and access) Promethazine 25mg IM or IV[2] OR Diphenhydramine 50mg IM or IV[3]
6. Consider administration of **corticosteroids PO, IM, or IV** (choice to administer, route of administration, and dose is determined by investigator judgment based on severity of symptoms and presence of angioedema) Prednisone 30 to 60mg PO and taper over 5 to 7 days OR Hydrocortisone 100mg IV or IM OR Methylprednisolone 1 to 2mg/kg IV push or IM	**6.** Administer **corticosteroids IM or IV** (choice to administer, route of administration, and dose is determined by investigator judgment) Hydrocortisone 100mg IV or IM OR Methylprednisolone 1 to 2mg/kg IV push or IM
7. **Vital signs** per 15 minutes or more often if indicated	**7.** **Vital signs** per 15 minutes or more often if indicated
8. Take **picture** with participant consent	**8.** Take **picture** with participant consent
9. **Observe** for at least 2 hours	**9.** **Observe** to ensure more epinephrine / adrenaline or other intervention is not needed
10. **Discharge** if medically stable, improving, or resolution, with no new lesions. Arrange for participant transport, as needed (ie, if driving or using public transportation is not advisable per investigator judgment).	**10.** **Transfer to Emergency Room or Casualty Facility by ambulance as needed**
11. Provide or advise use of **oral antihistamine** (eg, Cetirizine) for 3 days	**11.** Continue **medications** (eg, oral antihistamines and/or steroids) as instructed at Emergency Room or Casualty Facility
12. Stay in **contact by telephone daily** for 2 days or until resolution	**12.** Stay in **contact by telephone daily** for 2 days or until resolution
NOTE: Specific medications and doses listed here are examples only. Investigators should apply their judgment to use the appropriate, locally available options. ***Some type of infusion reactions eg. dyspnea without rash, usually resolve spontaneously and may be managed by brief infusion pause and re-initiation of the infusion at a slower rate. For guidelines on slowing an infusion see Section 6.*** [1]Second generation antihistamine is preferred; [2]IV push slowly over 1 minute; [3]IV push slowly over 2 minutes	

Supplementary Appendix 2: Participants experiencing more than one IRR

ID	Trial	Infusion No.	Age	Sex at birth	Race	Severity Grade	Treatment Assignment	IRR Category	Discontinuation status
1	HVTN 703 / HPTN 081	1	24	Female	Black	Moderate	VRC01 10mg/kg	Other (nasal congestion, throat irritation and difficulty swallowing)	No change
1	HVTN 703 / HPTN 081	3	24	Female	Black	Moderate	VRC01 10mg/kg	Other (flushing and pruritus)	No change
1	HVTN 703 / HPTN 081	6	25	Female	Black	Mild	VRC01 10mg/kg	Urticarial reaction	Permanently Discontinued
2	HVTN 703 / HPTN 081	3	28	Female	Black	Moderate	VRC01 10mg/kg	Dyspnea without rash	No change
2	HVTN 703 / HPTN 081	9	29	Female	Black	Moderate	VRC01 10mg/kg	Urticarial reaction	Permanently Discontinued
3	HVTN 703 / HPTN 081	4	26	Female	Black	Moderate	VRC01 10mg/kg	Other reaction (Infusion related reaction)	No change
3	HVTN 703 / HPTN 081	5	26	Female	Black	Moderate	VRC01 10mg/kg	Dyspnea without rash	Permanently Discontinued
4	HVTN 703 / HPTN 081	2	33	Female	Black	Mild	VRC01 10mg/kg	Other (chest discomfort)	No change
4	HVTN 703 / HPTN 081	3	33	Female	Black	Mild	VRC01 10mg/kg	Dyspnea without rash	No change
5	HVTN 703 / HPTN 081	3	22	Female	Black	Mild	VRC01 10mg/kg	Dyspnea without rash	No change
5	HVTN 703 / HPTN 081	5	23	Female	Black	Mild	VRC01 10mg/kg	Dyspnea without rash	No change
5	HVTN 703 / HPTN 081	10	24	Female	Black	Mild	VRC01 10mg/kg	Other (flushing, throat irritation and continous coughing)	No change
6	HVTN 703 / HPTN 081	5	34	Female	Black	Mild	VRC01 10mg/kg	Other reaction (Infusion related reaction)	No change
6	HVTN 703 / HPTN 081	7	34	Female	Black	Moderate	VRC01 10mg/kg	Other reaction (Infusion related reaction)	No change
7	HVTN 703 / HPTN 081	3	23	Female	Black	Mild	VRC01 10mg/kg	Other reaction (Infusion related reaction)	No change
7	HVTN 703 / HPTN 081	4	23	Female	Black	Mild	VRC01 10mg/kg	Other reaction (Infusion related reaction)	No change
8	HVTN 703 / HPTN 081	4	33	Female	Black	Moderate	VRC01 10mg/kg	Other (itchy maculo-papular rash)	No change
8	HVTN 703 / HPTN 081	5	33	Female	Black	Mild	VRC01 10mg/kg	Urticarial reaction	Permanently Discontinued
9	HVTN 703 / HPTN 081	1	22	Female	Black	Mild	VRC01 10mg/kg	Other (generalised pruritus)	No change
9	HVTN 703 / HPTN 081	2	22	Female	Black	Severe	VRC01 10mg/kg	Urticarial reaction	Permanently Discontinued

10	HVTN 703 / HPTN 081	1	21	Female	Black	Mild	VRC01 30mg/kg	Other reaction (Infusion related reaction)	No change
10	HVTN 703 / HPTN 081	10	23	Female	Black	Mild	VRC01 30mg/kg	Dyspnea without rash	Not Applicable
11	HVTN 703 / HPTN 081	1	24	Female	Black	Mild	VRC01 30mg/kg	Other (erythematous rash on trunk)	No change
11	HVTN 703 / HPTN 081	2	24	Female	Black	Moderate	VRC01 30mg/kg	Urticarial reaction	Permanently Discontinued
12	HVTN 703 / HPTN 081	3	22	Female	Black	Mild	VRC01 30mg/kg	Other (flushing, chest discomfort and headache)	No change
12	HVTN 703 / HPTN 081	10	23	Female	Black	Mild	VRC01 30mg/kg	Other (flushing)	Not Applicable
13	HVTN 703 / HPTN 081	1	25	Female	Black	Moderate	VRC01 30mg/kg	Other (generalised pruritus)	No change
13	HVTN 703 / HPTN 081	3	26	Female	Black	Moderate	VRC01 30mg/kg	Other (generalised pruritus)	No change
13	HVTN 703 / HPTN 081	4	26	Female	Black	Moderate	VRC01 30mg/kg	Other (generalised pruritus)	No change
13	HVTN 703 / HPTN 081	5	26	Female	Black	Mild	VRC01 30mg/kg	Other (generalised pruritus)	No change
14	HVTN 704 / HPTN 085	1	24	Female	Multi-racial	Mild	VRC01 30mg/kg	Urticarial reaction*	No change
14	HVTN 704 / HPTN 085	2	24	Female	Multi-racial	Mild	VRC01 30mg/kg	Urticarial reaction	Permanently Discontinued
15	HVTN 703 / HPTN 081	4	35	Female	Black	Mild	Placebo	Other reaction (Infusion related reaction)	No change
15	HVTN 703 / HPTN 081	5	35	Female	Black	Mild	Placebo	Other (flushing, dizziness and continous coughing)	No change
16	HVTN 704 / HPTN 085	2	24	Male	Other	Mild	Placebo	Other reaction (Pruritus)	No change
16	HVTN 704 / HPTN 085	3	24	Male	Other	Mild	Placebo	Other reaction (Pruritus)	Permanently Discontinued

*Participant did not disclose that they had an urticarial reaction that developed at home post-infusion hence infusion was not discontinued then.

Supplementary Appendix 3: Proportions of infusions triggering an infusion related reaction by the cumulative number of received infusions.

	HVTN 704/HPTN 085			HVTN 703/HPTN 081		
Received Infusion #	**Number of Infusions**	**Number of IRRs**	**Proportion (%) (95% CI)**	**Number of Infusions**	**Number of IRRs**	**Proportion (%) (95% CI)**
1	2699	18	0.67 (0.42, 1.05)	1924	34	1.77 (1.27, 2.46)
2	2596	4	0.15 (0.06, 0.40)	1851	19	1.03 (0.66, 1.60)
3	2533	12	0.47 (0.27, 0.83)	1800	14	0.78 (0.46, 1.30)
4	2463	4	0.16 (0.06, 0.42)	1754	12	0.68 (0.39, 1.19)
5	2413	3	0.12 (0.04, 0.36)	1705	12	0.70 (0.40, 1.23)
6	2365	2	0.08 (0.02, 0.31)	1660	6	0.36 (0.17, 0.79)
7	2314	0	0.00 (0.00, 0.17)	1617	4	0.25 (0.10, 0.63)
8	2256	3	0.13 (0.05, 0.39)	1568	3	0.19 (0.07, 0.56)
9	2179	1	0.05 (0.01, 0.26)	1521	5	0.33 (0.14, 0.77)
10	2043	2	0.10 (0.03, 0.36)	1407	2	0.14 (0.04, 0.52)

Supplementary Appendix 4: Numbers of infusions triggering an infusion reaction by the cumulative number of received infusions and clinical phenotype.

	HVTN 704/HPTN 085					HVTN 703/HPTN 081				
		Number (%) of infusion related reactions					Number (%) of infusion related reactions			
Received Infusion #	**Number of Infusions**	**Urticaria**	**Dyspnea with Rash**	**Dyspnea without Rash**	**Other**	**Number of Infusions**	**Urticaria**	**Dyspnea with Rash**	**Dyspnea without Rash**	**Other**
1	2699	13 (0.48)	0 (0.00)	0 (0.00)	5 (0.19)	1924	24 (1.25)	0 (0.00)	0 (0.00)	10 (0.52)
2	2596	2 (0.08)	1 (0.04)	0 (0.00)	1 (0.04)	1851	7 (0.38)	0 (0.00)	5 (0.27)	7 (0.38)
3	2533	5 (0.20)	2 (0.08)	1 (0.04)	4 (0.16)	1800	0 (0.00)	1 (0.06)	3 (0.17)	10 (0.56)
4	2463	3 (0.12)	0 (0.00)	1 (0.04)	0 (0.00)	1754	3 (0.17)	0 (0.00)	1 (0.06)	8 (0.46)
5	2413	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.12)	1705	3 (0.18)	0 (0.00)	5 (0.29)	4 (0.23)
6	2365	1 (0.04)	0 (0.00)	1 (0.04)	0 (0.00)	1660	1 (0.06)	0 (0.00)	2 (0.12)	3 (0.18)
7	2314	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1617	1 (0.06)	0 (0.00)	2 (0.12)	1 (0.06)
8	2256	1 (0.04)	0 (0.00)	1 (0.04)	1 (0.04)	1568	1 (0.06)	0 (0.00)	0 (0.00)	2 (0.13)
9	2179	1 (0.05)	0 (0.00)	0 (0.00)	0 (0.00)	1521	1 (0.07)	0 (0.00)	2 (0.13)	2 (0.13)
10	2043	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.10)	1407	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.14)