**Supplemental Table S1. Virus inoculations**

| Virus strain | Dose | Regimen |
|---|---|---|
| SIVmac251 | 100 $AID_{50}$[a] | Single inoculum intravenous (i.v.) |
| SIVmac239 | 1000 $TCID_{50}$[b] | Single inoculum, i.v. |
| SIVmac239/316e* | 1000 $TCID_{50}$ | Single inoculum, i.v. |
| SIVmac239ΔGY | 350 $TCID_{50}$ or 100 $TCID_{50}$ | Monkey DD87: 8 weekly challenges of 350 $TCID_{50}$ intra-vaginal (i.vag.)<br>Monkey DT18: single inoculum of 100 $TCID_{50}$, i.v. |
| SIVmac239ΔNef | 100 $TCID_{50}$ | Single inoculum, i.v. |
| SHIV89.6P | 1000 $TCID_{50}$ | Single inoculum, i.v. |
| SIV0302-2 | 1000 $TCID_{50}$ | Single inoculum, i.v. |

[a] $AID_{50}$: 50% Animal infectious dose

[b] $TCID_{50}$: 50% Tissue culture infectious dose

**Supplemental Table S2. Antibodies used for staining and flow cytometry**

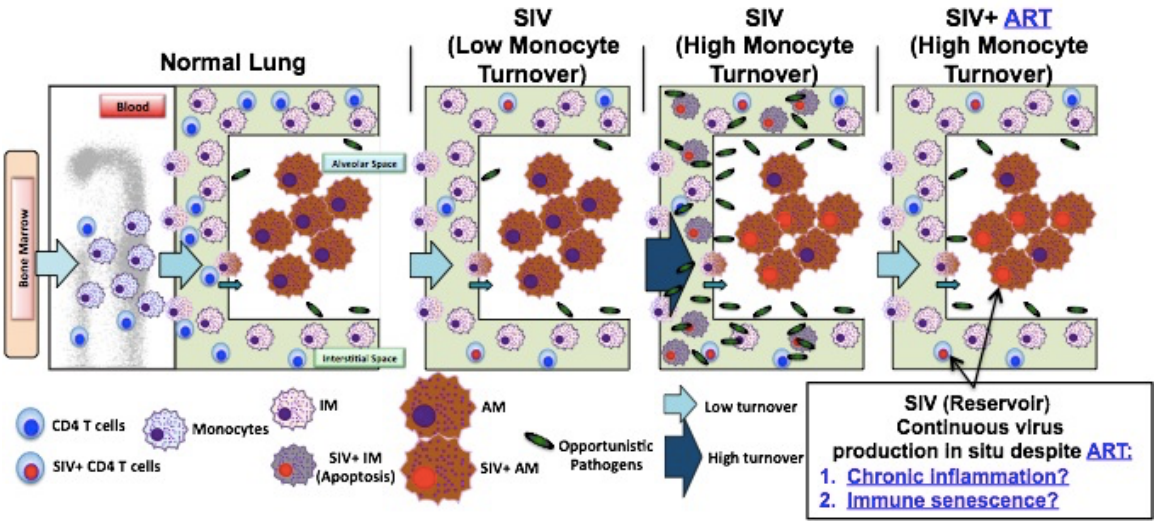
| Antibody | Clone | Fluorochrome | Vendor | Staining Panel |
|---|---|---|---|---|
| BrdU | 3D4 | FITC | BD | I, II, III, IV |
| CD1c (BDCA-1) | APC | APC | Miltenyl Biotec | I |
| CD11b | ICRF44 | AL700 | BD | II, III |
| CD11c | 3.9 | APC | eBioscience | III |
| CD14 | RMO52 | ECD | BD | II, III |
| CD14 | M5E2 | PB | BD | I |
| CD16 | 3G8 | V500 | BD | III |
| CD16 | 3G8 | APC-H7 | BD | I, III |
| CD123 | 7G3 | PCP-Cy5.5 | BD | I, II |
| CD163 | Mac 2-158 | PE | Trillium | I, II, III |
| CD20 | 2H7 | eFluor 450 | eBioscience | II, III |
| CD206 | 19.2 | APC | BD | II |
| CD206 | 15.2 | APC-Cy7 | Biolegend | III |
| CD3 | SP34-2 | Pacific Blue | BD | II, III |
| CD4 | L200 | PCP-Cy5.5 | BD | II, IV |
| CD8 | SK1 | V500 | BD | II |
| CD8 | M-T807 | QDot655 | NHP Reagent | I, III, IV |
| CD95 | DX2 | PB | Ebioscience | IV |
| HLA-DR | L243 (G46-6) | PE-Cy7 | BD | I, II, III, IV |
| CD11c | 3.9 | AL700 | eBioscience | I |
| CD3 | SP34-2 | V500 | BD | I |
| CD20 | B9E9 | ECD | Beckman Coulter | I |
| CCR5 | 3A9 | PE | BD | IV |
| CD28 | CD28.2 | ECD | Beckman Coulter | IV |
| CD3 | SP34-2 | AL700 | BD | IV |
| CD20 | L27 | APC-H7 | BD | IV |
| CCR7 | 150503 | V450 | BD | IV |

Note: Antibody panels I and IV were used to stain whole blood or PBMC, antibody panels II, III, and IV were used to stain lung biopsy or BAL samples.

**Supplemental Table S3. RNA *in situ* hybridization to detect SIV in AM and IM of lung tissues from infected monkeys.**

| Group of SIV-Infected NHP[+] | Number of animals exhibiting SIV-infected macrophage populations / total number of animals examined | | |
|---|---|---|---|
| | **AM** | **IM** | **AM & IM** |
| Low monocyte turnover rate (≤ 30%) | 1/3 | 1/3 | 2/3 |
| High monocyte turnover rate (>30%) | 5/6 | 5/6 | 5/6 |

[+]Nonhuman primates




**Supplemental Figure S1. Proposed mechanism of AIDS pathogenesis in the lung of SIV-infected macaques.** The lung contains at least two populations of macrophages; shorter-lived interstitial macrophages (IM) and longer-lived alveolar macrophages (AM). In this model, IM become massively infected with SIV and undergo a high rate of cell death that correlates with increased blood monocyte turnover. Conversely, SIV infection of the longer-lived AM does not lead to high rate of death compared to that of IM. ART is expected to successfully block or inhibit SIV infection in IM infection but not in SIV-infected longer-lived AM. Elimination of SIV-infected longer-lived AM, as well as SIV-infected CD4+ T cells, may be crucial for complete removal of SIV/HIV reservoirs to cure infection and safely discontinue ART.