Supplemental Figure 1: RhCMV/SIV vectors establish and indefinitely maintain high frequency SIV-specific T cell responses in diverse tissues: The figure shows the mean frequency (± SEM) of SIVgag-specific T cell responses within the CD4+ and CD8+ memory populations of the indicated tissues studied at necropsy of 4 RM that were given RhCMV(gag) vector twice – an initial inoculation 6.5 - 8.4 years prior to necropsy and a boost inoculation 4.4 - 5.8 years prior. Response frequencies were determined by intracellular expression of TNF and/or IFN-γ after stimulation with overlapping SIVgag peptides [PBMC = peripheral blood mononuclear cells; LN = lymph node; BAL = broncho-alveolar lavage lymphocytes].
Supplemental Figure 2: Confirmation of RhCMV/SIV vector super-infection and persistence in Group A and B RM. Urine was collected at 358 days post-initial vector inoculation from each of the RhCMV/SIV vector-vaccinated RM, and SIVgag, rev/tat/nef, pol and env expression was detected from co-cultured virus by immunoblot (a, Group A; b, Group B). Urine from DNA/Ad5-vaccinated RM (c, Group C), collected at the same time, was analyzed in parallel as a negative control. Each study RM is identified by its specific animal number (top). A known positive urine from another pan-RhCMV/SIV vector-vaccinated RM (RhCMV-SIV) was included in the Group C blots as a positive control. α-SIV Gag, Rtn, Pol and Env indicates the antibody specific for the designated protein. The molecular weight in kDa is shown at the left. Note that all Group A and B RM secrete each of the administered RhCMV/SIV vectors in urine.
Supplemental Figure 3: Comparative analysis of the development of vaccine-elicited T cell responses in Group A-C RM. a, Mean frequencies (± SEM) of SIVgag + rev/ nef/tat + env + pol-specific, CD4+ and CD8+ T cells and RhCMV-specific, CD4+ T cells within the peripheral blood memory compartment of Group A-C RM throughout the vaccine phase. Response frequencies determined by intracellular expression of TNF and/or IFN-γ after stimulation with overlapping SIV peptides (gag, rev/ nef/tat, env, pol) or RhCMV viral lysate, as described in the Methods. The SIV-specific response frequencies shown reflect the sum of responses to SIV proteins that were common to all vaccines (e.g., they exclude responses to vif and vpr/vpx, which were only included in the DNA and Ad5 vectors). Note that while the mean response frequencies at the end of the vaccine phase were similar between Groups A-C, the pattern of development for these responses differed with each vaccine. RhCMV/SIV vector administration was associated with a transient boost in RhCMV-specific CD4+ T cells (which occurred twice in Group A RM, and once in Group B RM). b, Mean frequencies (± SEM) of CD8+ memory T cells from the Mamu A*01+ RM in Groups A, B and C (n =4 for each group) that label with tetrarmers for the Mamu A*01-restricted epitopes gag-CM9 and tat-SL8. Note that CD8+ T cells specific for these 2 usually immunodominant SIV epitopes are induced by DNA and Ad5 vaccination, but are not elicited by RhCMV/SIV vectors, in keeping with our previous observations3 that the epitope targeting of RhCMV/SIV vectors is distinct from DNA vectors, conventional viral vectors, and SIV itself. Although the CD8+ T cell response to the gag-CM9 epitope has been associated with vaccine-mediated control of SIV replication3, the absence of this response in Group A RM indicate that any protection against SIV challenge observed in these animals cannot be attributed to this effect.
Supplemental Figure 4: Comparative analysis of SIV-specific CD4+ and CD8+ T cell responses in broncho-alveolar lavage lymphocyte (BAL) populations at the end of the vaccine phase in Group A-C RM: The figure compares the mean frequency (+ SEM) of the overall SIV-specific CD4+ and CD8+ T cell responses and the contribution of the designated SIV proteins to these total responses in the BAL memory compartments of Groups A, B and C RM at the end of the vaccine phase (average of response frequencies in samples from days 379, 392, 401 and 413 post first vaccination). These data correspond to the responses in the peripheral blood memory compartment presented in primary Fig. 1b. Responses were determined by intracellular TNF and IFN-γ analysis after stimulation with overlapping peptides for each SIV protein. The differences in total SIV-specific response frequencies among the 3 vaccine groups was determined to be non-significant (p = NS) by the Kruskal-Wallis test. Note that vif and vpr/vpx sequences were included in the DNA and Ad5 vectors, but not in the RhCMV vectors, so that the total SIV-specific T cell responses of Group B and C, but not Group A, RM includes responses to these proteins.
Supplemental Figure 5: Comparative analysis of the memory subset phenotype of vaccine-elicited, SIVgag-specific CD8+ T cell responses in Group A-C RM at the end of the vaccine phase (prior to SIV infection). The specific CD8+ T cell response to overlapping SIVgag15mer peptides was determined in PBMC by intracellular analysis of CD69 and TNF and/or IFN-γ expression, and the responding T cells were then analyzed for their cell surface expression of CD28 vs. CCR7, as previously described5. The fraction of the total SIVgag-specific response with a central memory (CD28+/CCR7+), transitional effector memory (CD28+/CCR7-) and a fully differentiated effector memory phenotype (CD28-/CCR7-) are shown. The differences in the distribution of these memory subsets within the gag-specific responses of RM in Groups A, B, C was highly significant (p < .0001) by Kruskall-Wallis analysis with pair-wise comparisons using the Wilcoxon test confirming that the responses of Group A and B RM were significantly different in subset distribution from Group C RM (p = .0011), but were not different from each other.
Supplemental Figure 6: Acquisition of SIV infection by Group A-D RM with repeated, limiting dose SIVmac239 challenge. The figure shows a Kaplan-Meier analysis of the number of challenges required to achieve infection in Group A-D RM with the onset of infection defined as the first plasma viral load $\geq$30 copy equivalents/ml. Although the median number of challenges required to achieve infection in Group A (n=12), B (n=12), C (n=9) and D (n=28) RM were 4, 4, 9 and 5, respectively, the Logrank test revealed a p value of 0.11, indicating that these acquisition curves were not significantly different.
Supplemental Figure 7: Comparative analysis of SIV pathogenesis (CCR5+, CD4+ T cell depletion) in Group A-D RM. The figure shows the kinetics and extent of CD4+ T cell depletion within the broncho-alveolar lavage (BAL) T cell compartment following infection of controllers (red) vs. non-controllers (black) among Group A-C and concurrent Group D controls. BAL CD4+ T cells are essentially 100% CCR5+ memory cells and thus serve as a sensitive indicator of CD4+ T cell depletion by CCR5-tropic SIVmac239. The significance of differences in average depletion from days 21-70 pi of Group A and B controllers vs. Group C was determined by the Wilcoxon rank sum test with the p values shown in the figure. RhCMV/SIV vector-vaccinated controllers (Group A and B) manifest no discernable CD4+ T cell depletion in BAL, in contrast to all RM with progressive infection, even DNA/Ad5-vaccinated (Group C) RM with significant, albeit partial, virologic control. Note that one Group A RM with initial complete virologic control lost control at day 77 post-infection (see primary Fig. 1c), and following the onset of progressive infection manifested profound CD4+ depletion. Note also that one Group D control RM manifested an initially non-progressive infection (“occult infection”: see primary Fig. 1c), which spontaneously transitioned to progressive infection at day 112 post-infection, at which point profound CD4+ T cell depletion in BAL was observed.
Supplemental Figure 8: Comparative analysis of cell-associated SIV DNA and RNA in Group A-D RM. The figure shows the level of cell-associated SIV DNA and RNA, as determined by standard (non-nested) quantitative real-time RT-PCR and PCR\textsuperscript{23,24}, in peripheral blood and lymph node mononuclear cells collected between 105 and 140 days pi for Group A and B controllers vs. Group A-D non-controllers, with the significance of differences between controllers and non-controllers determined by the Wilcoxon rank sum test.
Supplemental Figure 9: Control of SIVmac239 infection in RhCMV/SIV vector-vaccinated RM of Group A and B does not correlate with the differences in the intrinsic target cell infectivity mediated by expression of TRIM5 alleles with different B30.2(SPRY) domains. The 24 RhCMV/SIV-vaccinated RM of vaccine Groups A and B were genotyped with respect to TRIM5 alleles associated with different intrinsic susceptibility of target cells to SIVmac251 infection: low susceptibility = TRIM5 alleles 1-5 only; medium susceptibility = TRIM5 alleles 1-5 and 6-11; high susceptibility = TRIM5 alleles 6-11 only\(^{38}\). In keeping with the relative insensitivity of SIVmac239 replication to TRIM5 restriction\(^{39}\), the distributions of these genotypes were not significantly different between controllers and non-controllers (using Fisher's exact test).
Supplemental Figure 10: Vaccine-elicited SIV-specific CD4+ T cell response frequencies during the vaccine phase do not predict stringent control of SIV infection in vaccine Group A and B RM. Analysis of total SIV-specific CD4+ T cell responses as measured by intracellular cytokine analysis for TNF and/or IFN-γ in the blood memory compartment during the vaccine phase of Group A and B RM with differences in the magnitude of these responses between controllers (red) and non-controllers (black) at the designated time points (arrows) determined by Wilcoxon rank sum test. In contrast to SIV-specific CD8+ responses (primary Fig. 2a), the magnitude of the peak post-boost SIV-specific CD4+ response does not correlate with subsequent control of SIVmac239 challenge.
Supplemental Figure 11: Comparative analysis of the change in the SIVgag-specific CD4+ and CD8+ T cell response frequency in broncho-alveolar lavage lymphocytes (BAL) following controlled vs. progressive infection in Groups A, B and C RM. The figure shows the fold change in SIVgag-specific response frequencies in BAL following controlled infection of Group A and B RM and progressive infection of Group A, B and C RM. These data correspond to the same analysis of the peripheral blood memory compartment presented in primary Fig. 2c. Responses were determined by intracellular TNF and IFN-γ analysis after stimulation with overlapping peptides for the SIVgag protein. The significance of differences in peak response boosting between Group A vs. Group B in the controllers and Group A or Group B vs. Group C in the non-controllers was determined by the Wilcoxon rank sum test with the p values shown in the figure. Note that the CD4+ and CD8+ SIVgag-specific responses elicited by RhCMV/gag vectors alone (Group A) did not boost in BAL (or in blood; see primary Fig. 2c) in response to either controlled or progressive infection, consistent with a highly T\textsubscript{EM}-biased overall (systemic) population. These highly T\textsubscript{EM}-biased responses appear to manifest early protection (prior to systemic progression), but can not suppress viral replication once systemic, progressive infection ensues, likely related to this inability to expand when the SIV infection breaches the initial “line of defense”. Although Group B RM (RhCMV/SIV followed by Ad5/SIV vaccination) manifested an SIVgag-specific T cell population with T\textsubscript{EM} dominance (by phenotype, Suppl. Fig. 5 and early protection, primary Fig. 1c), these RM clearly retained an Ad5 vaccine-associated T\textsubscript{CM} component (likely in lymph node) that allowed them to boost response frequencies in blood and BAL after infection, particularly progressive infection. Thus, Group B RM manifested the early protection characteristic of RhCMV/SIV vector-elicited T\textsubscript{EM}, yet retained the ability to suppress, at least transiently, systemic viral replication in progressive infection, the latter likely related to the ability to expand and deliver additional effectors to sites of SIV replication.
Supplemental Figure 12: RhCMV/SIV vector-vaccinated controllers manifest robust T cell responses to SIVvif protein. SIVvif was included in the Ad5/SIV vector set, but not the RhCMV/SIV vector set, and therefore Group B RM, but not Group A, RM manifested a (T<sub>CM</sub>-biased) CD4+ and CD8+ T cell response to this protein during the vaccination phase of the experiment, prior to the onset of SIV infection after challenge. The figure shows that SIVvif-specific, CD4+ and CD8+ T cell responses are induced (Group A) or boosted (Group B) in controlled (non-progressive) infection to a similar extent as observed among Group D RM with progressive infection. These data confirm SIV infection in these controller RM, as described<sup>5</sup>, and demonstrate the reactivity of the naïve (Group A) or T<sub>CM</sub> (Group B) compartments in response to this infection. Responses were determined by intracellular TNF and IFN-γ analysis after stimulation with overlapping peptides for the SIVvif protein.
Supplemental Figure 13: CD4+ T cell depletion with mAb huOKT4A does not impact the viral-host equilibrium in Group A and B controllers. The figure shows the effect of mAb huOKT4A treatment on circulating CD4+ T cell counts, SIV replication and level of SIVvif-specific CD8+ T cells in broncho-alveolar lavage lymphocytes (BAL) in 4 RhCMV/SIV vector-vaccinated controllers (2 Group A and 2 Group B RM) vs. 2 conventional controllers (1 Group C, DNA/Ad5-vaccinated controller; 1 Group D spontaneous controller). This experiment was performed in parallel with the CD8+ lymphocyte depletion experiment with mAb cM-T807 shown in primary Fig. 3a, but used different RM. SIVvif-specific, CD8+ T cell response frequencies in BAL were measured as an exquisitely sensitive immunologic indicator of increasing viral replication. As shown in this figure, administration of the anti-CD4 huOKT4A mAb resulted in an initial transient suppression of viral replication in the partial controllers due to CD4+ target cell depletion and/or the direct anti-viral activity of the anti-CD4 mAb\(^{40}\), which was followed by a rebound of viremia associated with a boost in the SIVvif-specific CD8+ T cell response. In contrast, there was no such effect on the viral-host equilibrium in Group A and B controllers, as huOKT4A administration had no impact on either viremia or anti-SIVvif CD8+ T cell responses in these RM.
Supplemental Figure 14: The transient CD8+ T cell depletion associated with administration of the anti-CD8α mAb cM-T807 is typically complete in blood, but incomplete in tissues. The figure shows the course of CD8+ T cell depletion after the designated course of treatment with cM-T807 (the same protocol used in the experiment reported in primary Fig. 3a) in the peripheral blood, peripheral lymph node (LN) and the broncho-alveolar lavage (BAL) T cell compartments of 8 healthy RM. Note that residual CD8+ T cells are detectable in BAL and LN. These residual cells are coated with the cM-T807 mAb, but can be visualized with an anti-CD8 mAb to a non-cross-reactive epitope. The extent to which the cM-T807 binding compromises in vivo CD8+ T cell function remains to be determined.
Supplemental Figure 15: RhCMV/SIV vectors maintain high frequency CD4+ T cell responses to SIV proteins included in the vectors (gag/pol) in controller RM, whereas responses elicited by the SIV infection itself (vif) wane over time. The figure shows analysis of the frequencies of CD4+ T cells specific for SIV proteins that were (gag, pol) or were not (vif) included in the RhCMV/SIV vectors in the peripheral blood of 4 Group A “controllers” for which long-term data is available. These data correspond to the same analysis of the CD8+ T cell responses to these SIV proteins presented in primary Fig. 3b. Responses were determined by intracellular TNF and IFN-γ analysis after stimulation with overlapping peptides for the designated SIV protein, and in this analysis were normalized to the response frequencies immediately prior to SIV infection for SIV Ags included in the vaccine (gag, pol), or to the peak frequencies following SIV infection for the SIV Ags not included in the vaccine (vif). The 4 Group A controllers used in this long-term response analysis include those subjected to transient CD4+ or CD8+ lymphocyte depletion (2 RM for CD8; the other 2 for CD4; primary Fig. 3a and Suppl. Fig. 13). As Ag-specific CD4+ responses cannot be reliably determined during the period of overall CD4+ lymphocyte depletion, these periods are shown as gaps for the 2 affected RM in this profile. Despite these gaps, it is clearly evident the SIVgag- and SIVpol-specific CD4+ T cells are maintained at pre-infection frequencies over the long term in controller RM, consistent with their maintenance by the persistent RhCMV vectors. In contrast, the SIVvif-specific CD4+ T cell responses, elicited by the SIVmac239 infection itself, waned over time, consistent with the extreme paucity or absence of vif Ag in these stringent SIVmac239 controllers. The significance of differences in the maintenance of response frequencies of gag- and pol- vs. vif-specific CD4+ T cells in these RM was determined by Wilcoxon rank sum analysis with the p value shown in the figure.
### SUPPLEMENTAL TABLE

| RM #  | Cohort | Axillary Lymph Node | Inguinal Lymph Node | Submandibular Lymph Node | Tracheobronchial Lymph Node | Iliosacral Lymph Node | Sup. Mesenteric Lymph Node | Med. Mesenteric Lymph Node | Inf. Mesenteric Lymph Node | Ileocecal Lymph Node | Spleen | Liver | Thymus |
|-------|--------|---------------------|---------------------|--------------------------|----------------------------|-----------------------|---------------------------|---------------------------|--------------------------|------------------------|--------|-------|--------|
| 24102 | Group A| 0/20                | 0/20                | ND                       | 0/20                       | 0/20                  | 0/20                      | ND                        | 0/20                     | ND                     | ND     | ND    | ND     |
| 24115 | Group B| 0/20                | 0/20                | ND                       | 0/20                       | 0/20                  | ND                        | 0/20                      | ND                       | 0/20                   | ND     | ND    | ND     |
| 23833 | Group B| 0/20                | 0/20                | ND                       | 0/20                       | 0/20                  | 0/20                      | ND                        | 0/20                     | 0/20                   | ND     | ND    | ND     |
| 24730 | Group B| 0/20                | 0/20                | 0/20                     | 0/20                       | 0/20                  | 0/20                      | 0/20                      | 0/20                     | 0/20                   | ND     | ND    | ND     |
| 23003 | LAV    | 20/20               | 20/20               | 16/20                    | 14/20                      | 8/20                  | 12/20                     | 9/20                      | 7/20                     | 13/20                  | 8/14    | 5/20  |        |
| 24774 | Group C| 12/20               | 5/20                | 8/20                     | 6/20                       | 12/20                 | 9/20                      | 14/20                     | 9/20                     | 6/20                   | 12/20  | 5/20  |        |

**Supplemental Table 1:** Infectious SIV is not detectable in tissues of RhCMV/SIV vector-vaccinated controllers by inductive co-culture. The presence of inducible, replication competent virus was examined in the designated tissues obtained at necropsy from the same RM studied in primary **Fig. 4** with ultrasensitive nested quantitative PCR and RT-PCR -- 4 RhCMV/SIV vector-vaccinated controllers (1 Group A; 3 Group B) vs. 2 RM with conventionally controlled SIV infection (1 Group C controller; one live attenuated SIV-vaccinated – LAV – controller RM). Mononuclear cells isolated from these tissues were co-cultivated with CEMx174 cells for 13 and 17 days, followed by flow cytometric enumeration of SIVgag-expressing CEMx174 cells, as described\(^{16,36}\). Data is presented as the number of positive co-culture replicates out of the total number of replicates performed on that tissue (ND = no data).
SUPPLEMENTAL DISCUSSION

Commentary on potential mechanisms of RhCMV/SIV vector-associated protection: The partial, often transient viral control associated with conventional prime-boost T cell vaccines is likely due to anti-viral cytolytic activity mediated by anamnestic CD8+ T cell responses which intercept the developing infection after the onset of systemic replication\(^3,11-13,41\). The mechanism(s) by which RhCMV/SIV vector-elicted immune responses mediate their unique pattern of protection are more uncertain. The nature of the SIV-specific responses elicited by these vectors (e.g., robust and long-lasting CD4+ and CD8+ T\(_{EM}\) responses with little to no Ab response), as well as the immediate and sustained pattern of stringent protection observed, strongly argue for a T\(_{EM}\)-mediated mechanism that intercepts the developing SIV infection early and maintains anti-SIV activity indefinitely. While we cannot formally rule out the possibility that RhCMV vector-triggered innate immune responses contribute to protection, considerations arguing against this possibility include the following: 1) all study RM are chronically infected with a wildtype RhCMV that is closely related to the RhCMV/SIV vectors and thus would be expected to stimulate and maintain comparable innate immune responses and/or changes in NK cell receptor repertoire; 2) protection can initiate over 500 days following vector administration\(^5\) and can be maintained for >700 days pi (this study); and 3) general innate immune activation typically enhances, rather than suppresses, SIV infection\(^42,43\). We originally hypothesized that RhCMV/SIV vector-mediated protection reflected immune-mediated control, or possibly, abrogation of infection at the mucosal portal of entry\(^5\). The more extensive analysis in this study show that SIV and SIV-infected cells can escape the portal of entry and persist for months, if not longer, in protected RM. These new observations indicate that virologic control in these RM is not restricted to the portal of entry, but is also both systemic and ongoing. The correlation between the peak magnitude of the SIV-specific CD8+ T cell response in the vaccine phase and the extent of subsequent SIV control supports a major role for CD8+ T\(_{EM}\) in protection, but does not rule out participation by CD4+ T\(_{EM}\) in either the initiation or maintenance of the protected state. It remains to be determined whether CD8+ and/or CD4+ T\(_{EM}\) control SIV via cytotoxicity, indirect mechanisms such as secretion of anti-viral cytokines, or both.
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