Supplemental Information

Identification of Interferon-Stimulated Genes with Antiretroviral Activity

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Infectivity/yield (% of screen average)

Figure S1
Fig S1. Effects of human and macaque ISGs on vector production and primate lentiviruses (Related to Figure 1).
(A) Effects of ISG encoding vectors on vector transduction in MT4 and THP-1 cells.
(B, C) Effects of ISGs in incoming screens with SIVmac (B) in MT4 and THP-1 cells; and SIVagmTAN, (C) in MT4 cells only, and effects of the same ISGs on the generation of infectious SIVmac (B) and SIVagmTAN (C) particles in 293T cells.
(D, E) Comparison of the effects of human and macaque ISGs (genes in both libraries) in incoming screens with HIV-1 (D) and SIVmac (E) in MT4 and THP-1 cells, and effects of the same ISGs on the generation of infectious HIV-1 (D) and SIVmac (E) from 293T cells. All screens were normalised to the screen average (100 arbitrary units).
Figure S2. Heat map representing effects of human ISGs on retroviral infection (Related to Figure 1 and Figure 2). The effect of ISGs in the 25 incoming and outgoing screens represented in a heat map. All screens were normalised to the screen average (100 arbitrary units) with inhibition indicated in red and enhancement in green. Absent data, due to inefficient transduction, is indicated in grey (ND). Where allelic variants, spliced variants and repeated genes occur in the library, all data is presented and represent separate values from distinct transduction/transfection events. Asterisks denote clusters of ISGs whose protective effect is most evident in THP-1 cells. Heatmaps were produced using Gitools 2.2 and genes were hierarchically clustered using Manhattan maximum distance.
Figure S3. Heat map representing effects of macaque ISGs on retroviral infection (Related to Figure 1 and Figure 2). The effect of ISGs in the 25 incoming and outgoing screens represented in a heat map. All screens were normalised to the screen average (100 arbitrary units) with inhibition indicated in red and enhancement in green. Absent data, due to inefficient transduction, is indicated in grey (ND). Where allelic variants, spliced variants and repeated genes occur in the library, all data is presented and represent separate values from distinct transduction/transfection events. Asterisks denote clusters of ISGs whose protective effect is most evident in THP-1 cells. Heatmaps were produced using Gitools 2.2 and genes were hierarchically clustered using Manhattan maximum distance.
Figure S4
Figure S4. Heat map comparing effects of human and macaque ISGs on retroviral infection (Related to Figure 1 and Figure 2). The effect of ISGs present in both human and macaque libraries in the 25 incoming and outgoing screens represented in a heat map (human left, macaque right for each screen). All screens were normalised to the screen average (100 arbitrary units) with inhibition indicated in red and enhancement in green. Absent data, due to inefficient transduction, is indicated in grey (ND). Where allelic variants, spliced variants and repeated genes occur in the library, all data is presented and represent separate values from distinct transduction/transfection events. Heatmaps were produced using Gitools 2.2 and genes were hierarchically clustered using Manhattan maximum distance.

a Multiple library copies (PSMB8, IFI16, GBP1, NRN1, RNF24, THN, TNFSF10, TNFSF13B, IRF7, HSPE, PXK, BTN3A3, SAMHD1, IFI16, PLEKHA4, MOV10, BUB1, IFI44L, ANKFY1, LY6E, ISG20, STARD5, SCO2, AIM2, IFI35, CASP7, XAF1, USP18, PABPC4, RARRES3, PNPT1, MASTL, TREX1, PPM1K, CCNA1, TAGAP, PRKD2, C1S, ADAMDEC1, FLJ23556, cGAS, ADAR, XRN)
Figure S5
Figure S5. 1MT and L-Trp do not affect HIV-1 replication without IDO1 induction or IFNγ treatment (Related to Figure 4 and Figure 5).

(A, B) Effects of 1-MT (A) or L-Trp (B) on the yield of infectious HIV-1 particles during a single cycle of HIV-1 replication in control MT4 cells (containing doxycycline inducible TagRFP)

(C) The yield of infectious progeny virions from a single cycle of HIV-1 replication in A549 cells without IFN-γ treatment in the presence of 50 µg/ml L-Trp or 100 µg/ml 1-MT

(D) As in C with TZM-bl cells, using 33 µg/ml L-Trp (TZM-bl cells) or 100 µg/ml 1-MT. Titers are mean±SD
**Figure S6**

(A) Western blots showing expression of various HIV proteins with different plasmid concentrations.

(B) Titration of TRIM56 plasmid (ng) showing a decrease in Titer (IU/ml) with increasing plasmid concentration.

(C) Comparison of cells and virions expression at different plasmid concentrations.

(D) Graph showing virion p24 (a.u.) with different plasmid concentrations.

E) Bar chart showing virion p24 (a.u.) at 0.5 and 0.25 TRIM56 plasmid ng.
Figure S6. Effects of TRIM56 on HIV-1 replication (Related to Figure 6).
(A) Western blot analysis of HIV-1 Gag, Env and TRIM56 expression and particle release following transient cotransfection of 293T cells with HIV-1 proviral plasmids and increasing amounts of a TRIM56 expression plasmid.
(B) Western blot analysis of MLV Gag and TRIM56 expression and particle release following transient cotransfection of 293T cells with MLV GagPol and vector plasmids, along with VSV-G and increasing amounts of a TRIM56 expression plasmid.
(C) The yield of infectious HIV-1 virions from cells transfected in panel (A).
(D) The yield of infectious MLV virions from cells transfected in panel (B).
(E) Quantitation of virion associated p24 CA generated in a single cycle of infection of GHOSTX4 and GHOSTX4-TRIM56 cells. Titers are mean+SD
Figure S7. Induction of TRIM56 and ISG expression by IFNα (Related to Figure 7).
(A, B) Western blot analysis of TRIM56 protein levels in MT4-LTR-GFP cells treated with increasing doses of IFNα. A typical blot (A) and quantitation (B) is shown (B, mean ± SD).
(C, D) Microarray analysis of the expression levels (in arbitrary units, a.u.) of 500 genes induced by 25U/ml IFNα in unmodified MT4-LTR-GFP cells (X-axis) versus corresponding mean values (Y-axis) for clones of control (C, mean ± SD n=4) or TRIM56-knockout (D, mean ± SD, n=7) MT4-LTR-GFP cells. The diagonal dashed lines indicate positions on which data points would fall if values were equivalent in the two plotted datasets.
| Virus          | Plasmid(s)                                      | Reference(s)                          | Incoming screens | Outgoing a Screens |
|---------------|------------------------------------------------|---------------------------------------|------------------|--------------------|
| HIV-1         | pNHG (JQ585717)/VSV-G                           | (Wilson et al., 2012)                 | MT4, THP-1       | n/a                |
|               | pNL4.3 (M19921)                                 | (Adachi et al., 1986)                 | n/a              | MT4-TMZ b          |
| HIV-2         | Δ nefΔ env EGFP/VSV-G                           | (Hatzioannou et al., 2003)            | MT4, THP-1       | MT4                |
| SIVmac        | Δ nefΔ env EGFP/VSV-G                           | (Hatzioannou et al., 2003)            | MT4, THP-1       | MT4                |
| SIVagmTAN     | Δ nefΔ env EGFP/VSV-G                           | (Hatzioannou et al., 2003)            | MT4              | MT4                |
| FIV           | Gag-Pol/packageable genome /VSV-G               | (Kemler et al., 2002)                 | MT4              | MT4                |
| EIAV          | Gag-Pol/packageable genome /VSV-G               | (Mitrophanous et al., 1999)           | CRFK             | MT4                |
| MPMV          | pSARM-EGFP/VSV-G                                | (Newman et al., 2006)                 | MT4              | MT4                |
| HERV-K        | Gag-Pol/ΔK-rec/packageable genome /VSV-G        | (Lee and Bieniasz, 2007)              | MT4              | MT4                |
| MLV           | Gag-Pol/packageable genome /VSV-G               | (Soneoka et al., 1995) (Neil et al., 2001) | MT4              | 293T               |
| CERV-2/MLV    | CERV2/MLV chimeric Gag-Pol/packageable genome /CERV2-Env | (Perez-Caballero et al., 2008; Soll et al., 2010) | 293T             | 293T               |
| PFV a         | Δ belΔ bel3 2A-EGFP                              | (Bock et al., 1998; Schmidt and Rethwilm, 1995) | HT1080           | HT1080             |

* HEK 293T cells were used as producer cells for all outgoing screens with the exception of PFV, in which HT1080s were used.
* MT4 TMZ cells are a single cell clone derived from MT4 cells that encode an HIV-1 LTR-GFP reporter construct [T.M. Zang and P.D. Bieniasz, unpublished data and (Busnadiego et al., 2014)]
| SPECIES | ISG       | Antiretroviral? | TRANSDUCTION (MT4)* | TRANSDUCTION (THP-1)* |
|---------|-----------|----------------|---------------------|----------------------|
| Human   | MDA5      | IFN hit        | 44.10               | 13.32                |
| Human   | EIF2AK2   | YES            | 27.15               | 2.19                 |
| Human   | IFITM1    | No             | 71.05               | 8.65                 |
| Human   | RNASE4    | No             | 113.75              | 8.97                 |
| Human   | RNF24     | No             | 90.62               | 19.45                |
| Human   | SAT1      | No             | 7.71                | 1.06                 |
| Human   | BST2/THN  | YES            | 64.18               | 2.52                 |
| Human   | FLJ11286  | No             | 92.52               | 15.81                |
| Human   | APOBEC3G  | YES            | 0.36                | 0.66                 |
| Human   | TNFRSF10A | IFN Hit        | 29.82               | 2.98                 |
| Human   | CEACAM1   | YES            | 1.06                | 0.26                 |
| Human   | FU4       | No             | 104.85              | 15.74                |
| Human   | SLFN12    | YES            | 0.97                | 0.55                 |
| Human   | DCP1A     | No             | 91.00               | 14.00                |
| Human   | PARP12    | No             | 66.09               | 4.24                 |
| Human   | TLK2      | YES            | 56.61               | 4.60                 |
| Human   | TRIM56    | YES            | 14.48               | 12.29                |
| Human   | PLEXHA4   | No             | 105.49              | 11.93                |
| Human   | MAP3K14   | No             | 86.95               | 16.88                |
| Human   | SAT1      | No             | 1.26                | 3.29                 |
| Human   | ADAMDEC1  | YES            | 103.71              | 18.36                |
| Human   | OAS3      | YES            | 20.47               | 3.39                 |
| Human   | ABCA9     | No             | 22.80               | 0.44                 |
| Human   | SAMD9L    | No             | 0.60                | 2.14                 |
| Human   | PARP10    | No             | 36.86               | 5.24                 |
| Human   | HERC5     | No             | 99.01               | 13.15                |
| Human   | TGFBI     | IFN hit        | 103.58              | 19.06                |
| Human   | TNK2      | YES            | 61.26               | 7.06                 |
| Macaque | E1F2AK2   | YES            | 0.08                | 0.39                 |
| Macaque | PMAIP1    | No             | 61.49               | 2.23                 |
| Macaque | RNFL24    | No             | 84.49               | 10.76                |
| Macaque | RNFL24c   | No             | 74.24               | 4.16                 |
| Macaque | SAT1      | No             | 10.71               | 0.95                 |
| Macaque | BST2/THN  | YES            | 1.07                | 0.85                 |
| Macaque | BST2/THNc | YES            | 1.35                | 2.27                 |
| Macaque | APOBEC3G  | YES            | 63.62               | 17.99                |
| Macaque | TNFRSF10A | IFN Hit        | 20.51               | 1.97                 |
| Macaque | IRF7      | IFN Hit        | 101.11              | 12.11                |
| Macaque | IRF7a     | IFN Hit        | 93.61               | 3.73                 |
| Macaque | IRF7b     | IFN Hit        | 85.11               | 1.20                 |
| Macaque | CEACAM1   | YES            | 60.74               | 3.96                 |
| Macaque | SLFN12 (isoform 2) | YES | 0.85 | 1.31 |
| Macaque | PARP12    | No             | 85.36               | 5.61                 |
| Macaque | TLK2      | YES            | 22.75               | 12.77                |
| Macaque | MOV10     | YES            | 18.57               | 16.15                |
| Macaque | ISG20     | No             | 64.62               | 9.89                 |
| Macaque | IFIT5     | No             | 6.47                | 0.66                 |
| Macaque | DDX3X     | No             | 14.75               | 20.33                |
| Macaque | C5orf39   | YES            | 3.25                | 5.73                 |
| Macaque | UNCl93B1  | YES            | 100.11              | 12.26                |
| Macaque | ZNF295    | No             | 30.93               | 11.61                |
| Macaque | C6orf150  | YES            | 84.01               | 10.75                |
| Macaque | MLKL      | YES            | 8.92                | 0.23                 |
| Macaque | APOBEC3F  | YES            | 29.42               | 0.84                 |
| Macaque | APOBEC38c | YES            | 36.49               | 0.70                 |
| Macaque | RHOB      | No             | 3.18                | 3.91                 |
| Macaque | SAMD9L    | YES            | 3.32                | 63.70                |
| Macaque | BTN3A1    | YES            | 2.48                | 0.60                 |
| Macaque | APOBEC3B  | No             | 5.18                | 14.73                |

*Normalized transduction (% of screen average)

b Stimulated IFN/ISRE driven reporter activity (IFN hit), Appears (yes) or does not appear (No) in Table S1 (ISGs with antiretroviral activity)

c Multiple library copies (RNFL24, THN, IRF7, APOBEC3F)
### Table S3. Human ISGs subtracted due to ISRE or IFNβ promoter stimulation (Related to Figure 3)

| ISG     | IFNβ 293T* | IFNβ THP1* | ISRE 293T* |
|---------|------------|------------|------------|
| EPSTI1  | 9.87       | 1.59       | 0.50       |
| IL1R    | 0.73       | 24.71      | 0.65       |
| IRF1    | 11.41      | 1.33       | 74.83      |
| IRF7    | 1.40       | 0.91       | 65.14      |
| MAFF    | 0.68       | 1.46       | 6.83       |
| MAP3K14 | 365.11     | 39.42      | 49.44      |
| MAP3K5  | 1.72       | 34.32      | 0.20       |
| MDA5    | 10.88      | 1.16       | 51.38      |
| MYD88   | 192.01     | 44.87      | 1.75       |
| NOD2    | 22.38      | 6.88       | 0.55       |
| P2RY6   | 6.04       | 1.88       | 3.02       |
| RIG-I   | 3.80       | 1.12       | 6.12       |
| RIPK2   | 85.93      | 36.50      | 0.68       |
| RIPK2*  | 112.12     | 140.93     | 1.15       |
| TBX3    | 1.59       | 0.71       | 7.02       |
| TGFB1   | 21.40      | 1.25       | 0.69       |
| TLR7    | 0.64       | 15.66      | 1.74       |
| TNFRSF10A | 243.76   | 0.63       | 3.22       |
| TRIM25  | 43.36      | 85.06      | 0.06       |
| TRIM38  | 12.16      | 12.37      | 0.85       |

*a* Fold-activation of reporter gene expression  
*b* Two library copies (RIPK2)

### Table S4. Macaque ISGs subtracted due to ISRE or IFNβ promoter stimulation (Related to Figure 3)

| ISG     | IFNβ 293T* | IFNβ THP1* | ISRE 293T* |
|---------|------------|------------|------------|
| AIM2    | 0.92       | 22.92      | 1.06       |
| AIM2*   | 1.31       | 15.62      | 0.98       |
| IFI16   | 0.81       | 8.83       | 0.38       |
| IFNB1   | 0.75       | 1.31       | 62.74      |
| IRF1    | 11.56      | 0.85       | 63.34      |
| IRF7    | 2.24       | 9.49       | 29.32      |
| IRF7*   | 2.85       | 20.08      | 14.72      |
| MYD88   | 11.09      | 17.13      | 1.24       |
| PRKD2   | 0.99       | 7.39       | 0.46       |
| RIG-I   | 10.58      | 0.40       | 4.25       |
| TNFRSF10A | 28.80    | 0.63       | 5.64       |
| TRIM38  | 1.27       | 14.34      | 0.98       |
| TRIM5-5 | 1.17       | 7.88       | 1.06       |

*a* Fold-activation of reporter gene expression  
*b* Two library copies (AIM2 and IRF7)
| ISG* | Incoming Screens (Hs)* | Incoming Screens (Mm)* | Production Screens (Hs)* | Production Screens (Mm)* | Anti-SCRPSYd | Reported anti-retroviral activity* | Reference(s) |
|------|------------------------|------------------------|--------------------------|--------------------------|--------------|-----------------------------------|--------------|
| IDO1 | HIV-2(MT4)             | HIV-2(MT4)             | HIV-1, Herv-K             | HIV-1, Herv-K             | Yes          | Here                              |              |
| TRIM56 |                        |                        |                          |                          |              |                     |              |
| ADAMDEC1 | HIV-1(THP-1), HIV-2(THP-1) | HIV-2(THP-1) |                          |                          |              |                     |              |
| AKT3 |                        |                       |                          |                          |              |                     |              |
| ANGPTL1 |                        |                        |                          |                          |              |                     |              |
| APOBEC3A |                        |                        |                          |                          |              |                     |              |
| APOBEC3B |                        |                        |                          |                          |              |                     |              |
| APOBEC3F |                        |                        |                          |                          |              |                     |              |
| APOBEC3G |                        |                        |                          |                          |              |                     |              |
| APOL1 | EIAV, HERV-K           |                        |                          |                          |              |                     |              |
| APOL6 |                        |                        |                          |                          |              |                     |              |
| B4GALT5 |                        |                        |                          |                          |              |                     |              |
| BGLR |                        |                        |                          |                          |              |                     |              |
| BCL3 |                        |                        |                          |                          |              |                     |              |
| BIRC3 |                        |                        |                          |                          |              |                     |              |
| BLVR |                        |                        |                          |                          |              |                     |              |
| BST2/THN |                        |                        |                          |                          |              |                     |              |
| C17orf60 |                        |                        |                          |                          |              |                     |              |
| C2orf28 |                        |                        |                          |                          |              |                     |              |
| C5orf9 |                        |                        |                          |                          |              |                     |              |
| C9orf52 |                        |                        |                          |                          |              |                     |              |
| CASC7 |                        |                        |                          |                          |              |                     |              |
| CCR1 | EIAV                   |                        |                          |                          |              |                     |              |
| CD163 |                        |                        |                          |                          |              |                     |              |
| CD74 |                        |                        |                          |                          |              |                     |              |
| CDK11A |                        |                        |                          |                          |              |                     |              |
| CEACAM1 |                        |                        |                          |                          |              |                     |              |
| CEBPD |                        |                        |                          |                          |              |                     |              |
| CFAS |                        |                        |                          |                          |              |                     |              |
| CHMP5 |                        |                        |                          |                          |              |                     |              |
| CLEC2B |                        |                        |                          |                          |              |                     |              |
| CLEC4A |                        |                        |                          |                          |              |                     |              |
| CNP |                        |                        |                          |                          |              |                     |              |
| CPT1A |                        |                        |                          |                          |              |                     |              |
| CR1 |                        |                        |                          |                          |              |                     |              |
| C3CL2 |                        |                        |                          |                          |              |                     |              |
| EHD4 |                        |                        |                          |                          |              |                     |              |
| EIF2A |                        |                        |                          |                          |              |                     |              |
| ELF1 |                        |                        |                          |                          |              |                     |              |
| ENPP2 |                        |                        |                          |                          |              |                     |              |
| EPAS1 |                        |                        |                          |                          |              |                     |              |
| ETV7 |                        |                        |                          |                          |              |                     |              |
| EXT1 |                        |                        |                          |                          |              |                     |              |
| FAM46A |                        |                        |                          |                          |              |                     |              |
| FAM46B |                        |                        |                          |                          |              |                     |              |

* ISGs with anti-retroviral activity (Related to Figure 1, Figure 2, and Figure S1).

*Reference(s):* 
- (Berger et al., 2011) 
- (Yu et al., 2004) 
- (Wiegand et al., 2004) 
- (McLaren et al., 2015; Taylor et al., 2014) 
- (McLaren et al., 2015) 
- (Hishiki et al., 2007) 
- (Neil et al., 2008) 
- (Gao et al., 2013; Schoggins et al., 2014; Schoggins et al., 2015) 
- (Kuang et al., 2011; Pincetic et al., 2010) 
- (Wilson et al., 2012) 
- (Wilson et al., 2012) 
- (Debrnard et al., 2013) 
- (Deb and et al., 2001; Yoon et al., 2015) 
- (Leiden et al., 1992) 
- (Telenti and Johnson, 2012)
| Gene     | Expression Patterns                          | HIV-1 | HIV-2 | SIVmac | FIV | HERV-K | PFV | MLV | CERV-2 |
|----------|---------------------------------------------|-------|-------|--------|-----|--------|-----|-----|--------|
| FFAR2    | HIV-1, HIV-2, SIVmac, SIVagmTAN, FIV, EIAV, MPMV, HERV-K, PFV, MLV, CERV-2 | Yes   | No    | Yes    | No  | Yes    | No  | No  | No     |
| FKB5     | FIV                                         | No    | No    | No     | No  | No     | No  | No  | No     |
| FLJ23558 | HIV-1, SIVmac, FIV, CERV-2                  | No    | No    | No     | No  | No     | No  | No  | No     |
| FOXN2    | FIV                                         | No    | No    | No     | No  | No     | No  | No  | No     |
| GAK      | HIV-1, SIVmac, FIV, CERV-2                  | No    | No    | No     | No  | No     | No  | No  | No     |
| GALNT2   | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| GBP2     | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| GJA4     | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| HIST1H3D | HIV-1, SIVmac, SIVagmTAN                   | No    | No    | No     | No  | No     | No  | No  | No     |
| HPSE     | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| MDA5     | HIV-1, HIV-2, SIVmac, SIVagmTAN, FIV, EIAV | Yes   | No    | Yes    | No  | Yes    | No  | No  | No     |
| IFITM3   | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| IL1RN    | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| IL4I     | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| IRF9     | HERV-K                                     | No    | No    | No     | No  | No     | No  | No  | No     |
| LAMP3    | SIVmac                                     | No    | No    | No     | No  | No     | No  | No  | No     |
| LDL1     | EIAV                                       | No    | No    | No     | No  | No     | No  | No  | No     |
| LGALS9   | HIV-2, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| MACS     | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| MASTL    | HIV-1, SIVagmTAN                           | No    | No    | No     | No  | No     | No  | No  | No     |
| MCB      | HIV-1, SIVagmTAN                           | No    | No    | No     | No  | No     | No  | No  | No     |
| MIR5     | HIV-1, SIVagmTAN                           | No    | No    | No     | No  | No     | No  | No  | No     |
| MLKL     | HIV-1, SIVmac, SIVagmTAN, FIV, PFV, CERV-2 | Yes   | Yes   | Yes    | No  | Yes    | No  | No  | No     |
| MOV10    | HIV-1, SIVmac, SIVagmTAN, FIV, PFV, CERV-2 | Yes   | Yes   | Yes    | No  | Yes    | No  | No  | No     |
| Mx2      | HIV-1, SIVmac, SIVagmTAN, FIV, PFV, CERV-2 | Yes   | Yes   | Yes    | No  | Yes    | No  | No  | No     |
| NFIL3    | SIVmac                                     | No    | No    | No     | No  | No     | No  | No  | No     |
| NOS2A    | HIV-2, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| OAS3     | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| OASL     | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| PABPC4   | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| PAK3     | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| PBEF1    | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| PIM3     | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| PPM1K    | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| PRAP1    | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| RASGEF1B | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| RHOB     | HIV-1                                      | Yes   | Yes   | Yes    | No  | Yes    | No  | No  | No     |
| RN19     | HIV-2, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| SAMD9    | HIV-2, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| SCO2     | HIV-2, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| SLC15A3  | HIV-1, SIVmac, MPMV, CERV-2                | No    | No    | No     | No  | No     | No  | No  | No     |
| SLC16A4  | HIV-1, SIVmac, MPMV, CERV-2                | No    | No    | No     | No  | No     | No  | No  | No     |
| SLC2A12  | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| SLF2      | HIV-1, SIVmac                              | No    | No    | No     | No  | No     | No  | No  | No     |
| SP100    | SIVmac                                     | No    | No    | No     | No  | No     | No  | No  | No     |
| SQLE     | FIV                                         | No    | No    | No     | No  | No     | No  | No  | No     |
| STAT2    | SIVmac                                     | No    | No    | No     | No  | No     | No  | No  | No     |
| TAGAP    | SIVmac                                     | No    | No    | No     | No  | No     | No  | No  | No     |
| TDRD7    | HIV-1                                      | Yes   | Yes   | Yes    | No  | Yes    | No  | No  | No     |
| THBD     | HIV-1                                      | Yes   | Yes   | Yes    | No  | Yes    | No  | No  | No     |
| Gene | Virus | Parental Lineage | Response | Reference |
|------|-------|------------------|----------|-----------|
| TLK2 | EIAV  |                  | Yes      | Pasare and Medzhitov, 2005 |
| TLR1 | HIV-2 | THP-1            | PI       | (Pasare and Medzhitov, 2005) |
| TLR3 | SIVmac | THP-1           | SIVmac   | (Pasare and Medzhitov, 2005) |
| TLR7 | HIV-1 | THP-1            | PI       | (Pasare and Medzhitov, 2005) |
| TLR1 | HIV-1 | THP-1            | SIVmac   | (Pasare and Medzhitov, 2005) |
| TMEM173 | SIVmac | THP-1 | SIVmac   | (Pasare and Medzhitov, 2005) |
| TNFSF10 | PFV     |                | No       | Burdette et al., 2011 |
| TNK2 | HIV-1 | THP-1            | PI       | Pasare and Medzhitov, 2005 |
| TRAFD1 | EIAV    |                | No       | (Pasare and Medzhitov, 2005) |
| TREGX1 | SIVmac  |            | Yes      | (Pasare and Medzhitov, 2005) |
| TRIM34 | HIV-2 | MT4, THP-1      | FIV      | (Pasare and Medzhitov, 2005) |
| TRIM5 | HIV-1 | MT4, THP-1      | FIV      | (Pasare and Medzhitov, 2005) |
| TRIMCYP | HIV-2 | MT4, THP-1      | SIVmac   | (Pasare and Medzhitov, 2005) |
| ULK4 | HIV-1 | THP-1            | PI       | (Pasare and Medzhitov, 2005) |
| UNC84B (SUN2) | HIV-1 | THP-1            | PI       | (Pasare and Medzhitov, 2005) |
| UNC93B1 | HIV-1, SIVmac, SIVgagTAN, HERV-K, MLV, CERV-2 | HIV-1, HIV-2, SIVgagTAN, HERV-K, MLV, CERV-2, EIAV, MPMV | PI | (Pasare and Medzhitov, 2005) |
| USP18 | EIAV  |                  | No       | (Pasare and Medzhitov, 2005) |
| XAF1 | EIAV  |                  | No       | (Pasare and Medzhitov, 2005) |
| ZC3HAV1 | SIVmac | THP-1 | SIVmac | (Pasare and Medzhitov, 2005) |
| ZNF107 | SIVgagTAN |            | No       | (Pasare and Medzhitov, 2005) |
| ZNF313 | FIV    |                | No       | (Pasare and Medzhitov, 2005) |

*ISGs which stimulated the IFNβ or ISRE promoter (Figure 3 and Table S3 and S4) are subtracted from this list. Hyperlinks are to the UniProt entries of the human orthologue (not necessarily the isoform screened).

*Viruses inhibited by 3-fold or greater in incoming screens, cell type indicated in parenthesis for cases in which ISGs were tested in more than one screen.

*Viruses inhibited by 5-fold or greater in production screens.

*ISGs that affected titer/transduction of the SCRPSY vector (Figure S1 and Table S2) are indicated by “Yes”

*“PI” indicates genes reported to have pro-inflammatory activity such as activating anti-viral cytokine production/signaling

*Multiple library copies (TNFSF10, THN, TRIM5, PABPC4, TAGAP, APOBEC3F, APOBEC3B)
Extended Experimental Procedures

Cell lines
The feline CRFK cells, macaque FRhK4 and LLC-MK2 and adherent human HEK 293T, TE671 and TZM-bl cell lines were maintained in Dulbecco’s Modified Eagle’s Medium (DMEM) with 10% FBS and gentamicin. GHOSTX4 (a single cell clone of the original GHOSTX4R5 cell line obtained through the AIDS Reagent Program, Division of AIDS, NIAID, NIH from Dr. Vineet N. KewalRamani and Dr. Dan R. Littman) were maintained in DMEM supplemented with 2.5µg/ml puromycin, 50µg/ml hygromycin, and 500µg/ml G418. A549 cells were maintained in Ham’s F12/DMEM, all supplemented with 9% fetal bovine serum (FBS) and gentamicin. Suspension rhesus 221 cells (RPMI supplemented with IL-2 and 17% FBS) and human MT4 and THP-1 cells were maintained in RPMI supplemented with 10% FBS and gentamicin. MT4-LTR-GFP indicator cells were generated by transduction with a lentivirus derived from pSIR LTR-GFP, a self-inactivating MLV reporter construct containing a cassette in which hrGFP expression is driven by the HIV-1 LTR. A single cell clone was generated by limiting dilution and maintained in 2.5µg/ml puromycin. ISG-expressing MT4 and GHOSTX4 cell lines were modified using lentiviral vectors. Limiting dilution was also used to generate a panel of GHOSTX4 cells, modified to express TRIM56. IFNβ1/ISRE reporter cell lines represent cell clones modified using MLV-derived retroviral vectors.

Retroviruses
Replication competent proviral clones encoding GFP (PFV) or VSV-G-pseudotyped envelope minus derivatives of HIV-1 (NHG Δenv/Δenv-G), HIV-2 (Δenv EGFP/Δenv-G), SIVmac (Δenv Δenv Δenv EGFP/Δenv-G) and SIVagmTAN (Δenv Δenv EGFP/Δenv-G) or multi-plasmid VSV-G-pseudotyped vector systems FIV, EIAV, HERV-K, and MLV were used as described previously (Busnadiego et al., 2014; Kane et al., 2013; Wilson et al., 2012). The ‘CERV2’ virus was generated using a chimeric construct containing a full length CERV2 Gag gene that is a consensus of endogenous CERV2 Gag sequences found in the chimpanzee genome (Perez-Caballero et al., 2008), linked to an MLV Pol sequence. CERV2 virions generated by co-transfection of 5µg of chimeric CERV2/MLV Gag-Pol, 5µg of MLV packageable genome, and 5µg of CERV2 envelope (Soll et al., 2010). In follow up analyses, intact proviral clones for HIV-1 (NL4-3) (M19921) and HIV-2 (ROD10) or GFP-encoding HIV-1 pNHG (JQ585717) with GFP in place of nef were also used. Intact proviral clones were pseudotyped with VSV-G as indicated.

Construction of an ISG library from rhesus macaques
An HIV-1 based vector pSCRPSY-DEST used to express the ISGs was based on a previously described HIV-1 based vector, pV1/hrGFP (Zennou and Bieniasz, 2006). pSCRPSY-DEST (GenBank accession KT368137) consists of a minimal packageable HIV-1 genome containing all essential cis-acting sequences with Gateway attB and SfiI restriction sites inserted in place of Nef, and a TagRFP-2A-Puro8 cassette inserted in place of a deleted fragment containing gag, pol, vif and vpr genes. The vpu and env genes are also deleted or inactivated. Thus, cells transduced with pSCRPSY-DEST express HIV-1 Tat and Rev and any cDNA inserted into the DEST sequences from completely spliced ‘early’ HIV-1 transcripts, while TagRFP and PAC (Puro8) are expressed from a late, unspliced HIV-1 transcript PAC2ATagRFP where PAC and TagRFP proteins are separated by a FMDV 2A stop-start peptide. In pilot experiments this vector format minimized the number of cells that expressed the transduction marker (TagRFP) but did not express a gene inserted into the DEST sites (typically GFP).

Using the same criteria used to select human ISGs (Dittmann et al., 2015; Schoggins et al., 2011), primer pairs were designed to amplify ~600 different macaque genes by RT-PCR. In order to target genuine orthologous transcripts, multiple primer pairs were designed based on transcript variants of the most significant BLAST match of the rhesus macaque (M. mulatta) genome using human reference sequence ISGs as probes. Directional SfiI restriction sites and 4 additional nucleotides were appended to the forward SfiI oligos (5'-CTCTGGCCAGAGGGCCATG-3') and the final 3 nucleotides of the SfiI site provided Kozak consensus sequences for the macaque ISGs. The reverse oligo also contained 4 additional nucleotides (5'-TCTCGGCCAGAGGGCCCTTA-3') and were immediately followed by the reverse complement of the ISG stop codon (ochre/UAU in this example). Each oligo also contained ~25 nucleotides complementary to the macaque ISG target. In total 864 primer pairs were designed and subsequently synthesized by Operon. IFNα-stimulated (1000 units/ml) FRhK4, LL-CMK2 and 221 cells were used as a source of macaque RNA (M. mulatta) for cDNA synthesis (superscript III). Pooled RNA from cells stimulated for 4, 16 and 24 hours was used. Each gene was PCR amplified using Pfu polymerase and reactions that did not yield the expected amplicon were repeated using Taq polymerase. PCR amplicons were conventionally cloned into a Gateway® (Invitrogen) compatible entry vector modified to contain directional SfiI sites. ISGs were subsequently sequence verified (Genewiz). ISG ORFs were selected for the library that either matched the amino acid sequence of NCBI macaque entries or yielded at least two clones with identical amino acid sequences. Selected ORFs were subcloned into pSCRPSY-DEST and pcDNA-
DEST40 (Invitrogen) destination vectors using LR-clonase (Invitrogen). The previously described arrayed human ISG library (Schoggins et al., 2011) was extended to include a small number of highly IFNα-stimulated human ISGs based upon the initial criteria used previously (Schoggins et al., 2011) and our own microarray data (Kane et al., 2013; Neil et al., 2008). This extended human library (Dittmann et al., 2015) was similarly transferred into pSCRPSY and pcDNA-DEST40 using LR-clonase. Prior to screening, the identity of human and macaque ISGs was confirmed using restriction digest (all clones) and scatter sequencing of ~10% of the libraries.

**Screening ISGs for antiretroviral activity**

For incoming screens, ISG-encoding lentiviral vectors (SCRPSY) were generated by cotransfection of 293T cells using polyethyleneimine with 25ng HIV-1 Gag-Pol and 5ng VSV-G expression vectors, along with 250ng of each SCRPsy-based ISG expression vector in a 96-well plate format (0.35x10^5 cells/well). Thereafter, culture supernatants were used to transduce the relevant susceptible target cells (THP-1 cells were spinoculated for 1hr at 1600 rpm). Transduced ISG-expressing cells were challenged 48 hours later with a single dose of the GFP-encoding retroviruses or retroviral vectors using a MOI ~0.5. Cells were fixed 48h post-infection and the percentage of TagRFP+ and GFP+ cells determined by flow cytometry. In order to determine ISGs that inhibit SCRPsy production (Figure S1 and Table S4, S5), the fraction of ISG/TagRFP-expressing cells was expressed as a percentage of the mean value across all wells for the respective library (H. sapiens or M. mulatta) in the HIV-1 incoming screens.

For production screens, 293T cells were transfected in a 96 well format, using polyethyleneimine with 75ng of ISG expression plasmids (pcDNA-DEST40) along with 5ng VSV-G expression vector, and 70ng of plasmids that generated GFP-transducing retroviruses (HIV-1, HIV-2, SLVmac, and SLVagmTAN), or 5ng of VSV-G with 35ng of Gag-Pol expression plasmid and 35ng of packageable genome (EIAV, FIV, and MLV), or 35 ng of chimeric CERV2/MLV Gag-Pol, 35ng of packageable genome, and 35ng of CERV2-Env, or 7ng VSV-G with 50ng packageable genome, 8ng Gag-Pol, and 19ng K-Rec expression plasmids (HERV-K). At 48h after transfection, supernatants were harvested and used to challenge either MT4 cells (HIV-1, HIV-2, SLVmac, SLVagmTAN, EIAV, FIV, and MLV) or 293T cells (HERV-K and CERV2). For the PFV production screen, HT1080 cells were transfected with 75ng of ISG expression plasmids and 75ng PFV expression plasmid. At 48h post-transfection, cells were lysed by multiple freeze-thaws and lysates were used to challenge HT1080 cells. All cells were fixed 48h post-infection and the percentage of GFP+ cells determined by flow cytometry (see also Table S1).

For each ISG, the fraction of infected, ISG/TagRFP-expressing cells (incoming screens) or the yield of infectious virions (production screens) was expressed as a percentage of the mean value across all wells for the respective library (H. sapiens or M. mulatta) in a given screen, except the MPMV incoming screen, in which values are expressed as the mean value across each plate.

**IFNβ1 and ISRE reporter cell lines and expression screens therein**

We amplified the ISRE-Luc fragment containing 5 repeats of a canonical ISRE (ISRE - TAGTTTCACCTTCCC) from a plRE-Luc plasmid (Agilent technologies, PathDetect ISRE cis Reporting System) using primers containing BglII sites and inserted this cassette upstream of the CMV IE promoter of pQCXIN (Clontech), in which NeoR has been replaced with the blasticidin resistant gene, termed pQCXIB. The plasmid used to make the reporter cell (ISRE-GFP) was constructed by insertion of 5 copies of the ISRE followed by the EGFP coding region into the BglII site, upstream of the CMV IE promoter of pQCXIB. The IFN beta promoter (~125 to +22) was amplified from human genomic DNA using primer pairs containing KpnI at the 5’-end and HindIII at the 3’-end, respectively, and subcloned into pGL2-Luc (Promega). The IFN beta-Luc fragment was then amplified using primers containing BglII and subcloned into pQCXIB. To construct the reporter cells, we transduced 293T or THP-1, with a low multiplicity of infection (less than 0.1). After selection with blasticidin, limiting dilution and expansion, single clones were measured for luciferase activity upon IFNα treatment (for ISRE-GFP). Single responsive clones were chosen for the screening assays.

THP-1 and HEK 293T cells containing an IFN β-promoter-driven luciferase reporter were transduced with ISG libraries and luciferase activity measured 48hrs later with Luciferase Assay System (Promega E1501) using Modulus™ II (Turner BioSystems). To reflect total IFN β-promoter induction, these screens were not normalized and fold change is presented. The previously described arrayed human and macaque ISG libraries, mock treated or treated with 100 units/ml IFNα, and GFP+ and RFP+ cells enumerated 12 hours later using flow cytometry. To reflect ISRE activation per transduced cell, these ISRE screens were normalized. ISGs stimulating ISRE/IFNβ1 driven reporter expression by >5 fold (normalized to SCRPSY transduction levels) were excluded from further examination of the candidate 'directly acting inhibitors' of incoming retroviral infection and are listed in Table S2 and S3.

**Stable or inducible expression of individual ISGs for follow-up studies**
For constitutive expression of ISGs in follow up studies, a lentiviral vector CCIB was derived from CSGW by replacing sequences encoding GFP with a multi-cloning site followed by an IRES sequence and a blasticidin resistance cassette. The SFFV promoter was also replaced with a CMV promoter. A selection of genes that inhibited HIV-1 NL4-3 by 3-fold or more during an outgoing library screen were cloned into CCIB using SfiI, Pmel-NotI, Xmnl/Pmel-NotI, Pmel or NotI restriction site combinations. These genes included the human FFAR, SLC15A3, TRIM56, APOL6, TBX3, EHD4, MOV10, GJA4, UNC93B1, TNK2, CX3CL1, MKX, MARCK, EXT1, CEACAM1 and OAS3, and the macaque MLKL, SLFN12, GPR37, PAPBC4, C5ORF39, RHOB, SAT1, MOV10, GJA4 and UNC93B1. GHOSTX4 cell lines expressing each of the aforementioned ISGs that exhibited anti-HIV-1 activity in outgoing screens were generated by transduction with CCIB based viruses followed by selection with 5µg/ml blasticidin. A control cell line containing empty vector CCIB was similarly generated. Multiple single-cell clones of GHOSTX4 expressing TRIM56 cells were derived by limiting dilution, and the continued expression of CD4 and CXCR4 was verified using flow cytometry.

For doxycycline-inducible expression of ISGs, the modified tetracycline-inducible lentiviral expression vectors (pLKOΔ-Myc-TRIM5α-IP, pLKOΔ-Myc-TagRFP-IP, pLKOΔ-Myc-TRIM5α-IN, pLKOΔ-Myc-TagRFP-IN) have been previously described (Busnadiego et al., 2014). HsIDO1 was amplified from the human ISG library and cloned into the same lentiviral expression vectors to produce pLKOΔ-Myc-IDO1-IP and pLKOΔ-Myc-IDO1-IN using directional SfiI sites. Doxycycline-inducible cell lines were produced via transduction of MT4 cells with modified LKO-derived lentiviral vectors, and subsequent selection with puromycin (2 µg/ml, Sigma) or G418 (1 mg/ml, Promega) as previously described (Busnadiego et al., 2014). ISG expression was induced in these cell lines using doxycycline hyclate (125 ng/ml, Sigma) for 24 hours prior to viral challenge.

For further examination of the candidate 'directly acting inhibitors' of incoming retroviral infection, human and macaque ISGs that conferred >2-fold protection from HIV-1 or HIV-2 infection in any incoming screen were investigated for their ability to protect cells from incoming HIV. This ISG list was filtered to remove ISGs that activated ISRE/IFNB1 driven reporter expression by >5-fold. The remaining ISGs (Human ISGs AKT3, B2M, BCL3, C5orf39, CCD1C09B, CCL2, CCL4, CCL5, CDKN1A, CEBPD, cGAS, DDIT4, DEFB1, EPAS1, FAM46C, FBXO6, HPSE, IDO1, IFI30, IFITM3, IL15, IRF2, LGALS9, MXK, MT1H, Mx2, NOS2A, SCARB2, SP100, TRIM5, TRIM56 and UNC84B in addition to macaque ISGs AKT3, BCL3, BRDG1, BTN3A2, BTN3A2, BUB1, C1orf38, cGAS, CCNA1, CDKN1A, CHMP5, ELF1, GMPR2, IFI16, MDA5, IFITM3, IDO1, LDB1, LGALS9, LY6E, MXK, MT1E, Mx2, NAPA, PAK3, SAMD9, SAT1, SLC16A4, TLR1, TLR3, TLR7, TMEM140, TNFSF13B, TNFSF18, TRIM5-1, TRIM5-2, TRIM5-3, TRIM5-4 and TRIMCYP) were considered further and ISGs that conferred >2-fold protection in the follow up subscreen are displayed in Fig 3. Human APOBEC3A met the criteria but was not tested in the subscreen due to low transduction levels. Human C5orf39 and NOS2A were overly toxic in MT4 cells and were not considered further in this context. We were unable to achieve efficient transduction of THP-1 cells using vectors encoding macaque SAT1 and this gene was not considered further in this context.

CRISPR-mediated TRIM56 knockout
A derivative of the HIV based retroviral vector lentiCRISPR Version 2 (Addgene, Plasmid #52961) was constructed by replacing the puromycin resistance gene with a blasticidin resistance gene. TRIM56 CRISPR knockout constructs were made by inserting targeted guide sequences via BsmBI into the modified vector. The CRISPR guide sequences CR1 and CR3 were designed using the CRISPR design program available at http://crispr.mit.edu/ (CR1 targets TRIM56 bp171-191 CGAGTGCGCAGAGCATGTC; CR3 targets TRIM56 bp 183-203, CGACAGTGCGTGCGGCCGG). MT4-LTR-GFP knockout cells were derived by transduction with lentiCRISPRV2 based viruses followed by selection with 5µg/ml blasticidin. Single-cell clones derived from populations of cells transduced with control, CR1 and CR3 vectors were derived by limiting dilution and screened for strongly reduced or absent TRIM56 expression by western blotting. None of the control subclones exhibited reduced or absent TRIM56 expression.

Single cycle replication assays
For the incoming, single-cycle infectivity assays in the MT4 cells lines with doxycycline-induced IDO1, TRIM5α, or TagRFP expression and all titration experiments to determine infectious units in MT4 or MT4-LTR-GFP cells, cells were treated or not treated with doxycycline hyclate for 24h before viral challenge. At 16h post-infection, dextran sulfate was added to the HIV-1 (NHG) infected cells to limit infection to a single cycle. Cells were fixed 48h post-infection and the percentage of GFP+ cells determined by flow cytometry. For viral production assays, MT4 cell lines were treated or untreated for 24h with doxycycline hyclate before infection with HIV-1 (NHG or NL4-3) using a MOI of ~0.3 or HIV-2 (VSV-G pseudotyped ROD10) using an MOI of ~0.6. Cells were also treated with L-tryptophan (Melford) or 1-methyl-L-tryptophan (1-MT, Sigma-Aldrich) at the time of infection, as indicated. At 44h post-infection, cells were lysed in SDS sample buffer and virus-containing
and CRISPR knockout subclones that were untreated or treated with 25 U/ml IFN.

Microarray analyses
Scientific) anti-mouse/anti-rabbit antibodies labeled with IRDye® 800CW or IRDye® 680RD (LI-COR Biosciences or Thermo Scientific) and scanned using a Li-Cor Odyssey Scanner.

Microarray analyses
Total RNA was extracted, using the RNeasy Plus Mini kit (Qiagen), from MT4-LTR-GFP cells control subclones and CRISPR knockout subclones that were untreated or treated with 25 U/ml IFNα (Sigma) for 24 h before harvest.
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