Supporting Information

Varadarajan et al. 10.1073/pnas.1305066110

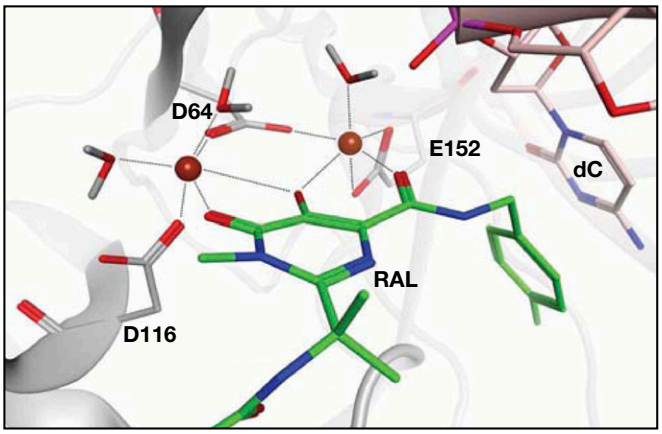

Fig. S1. Mechanism of inhibition by raltegravir (RAL). A model of the active site of HIV-1 intasome with RAL bound is shown. RAL and the DNA are shown as stick diagrams; RAL is in green, the DNA is pink. The protein is gray, with a ribbon backbone and stick side chains. The two bound Mg^{2+} are shown as red spheres. RAL binds the two Mg^{2+} ions in the active site, and the benzyl ring of RAL stacks on the nucleobase of the penultimate cytosine of the viral DNA.

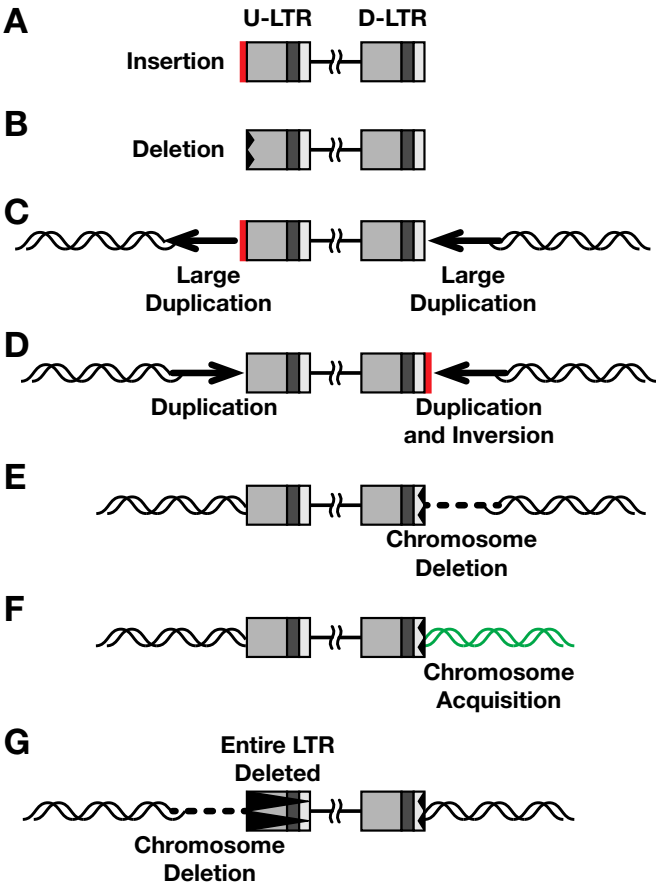

Fig. S2. Types of aberrant viral DNA ends and proviruses recovered from cells treated with RAL. Viral LTRs are shown as shaded boxes: the dark gray box represents the U3 region, R is shown by the black box, and U5 is indicated by the light gray box. (*A* and *B*) Types of viral DNA ends seen in the aberrant proviruses. (*A*) Insertion of additional bases at the viral DNA ends is indicated by a solid red box; (*B*) deletion from the viral DNA is indicated by a black jagged end. Deletion of the entire LTR is indicated by the jagged end stretching through the LTR. (*C*–*G*) Types of integrated proviruses. Large duplications of flanking host DNA are indicated by long bold arrows; the direction of the arrowheads indicates the orientation of the flanking host sequences. Acquisition of sequences from a different host chromosome is indicated by green DNA strands. Deletion of sequences from the host chromosome is indicated by a hashed line.

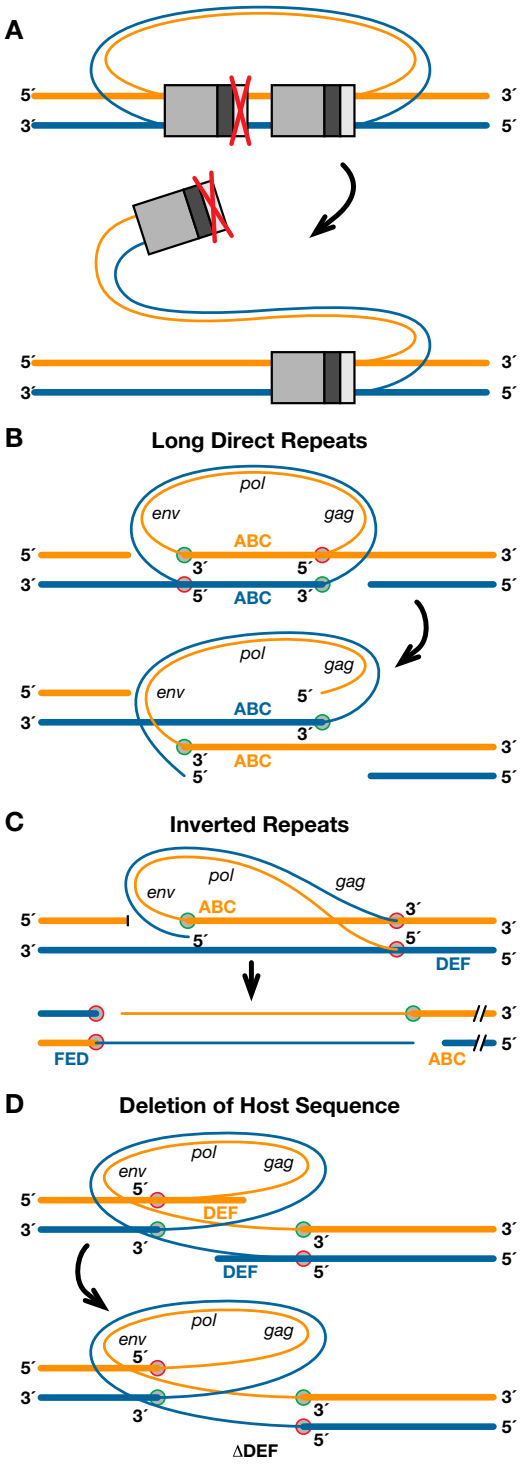

Fig. S3. Models for the generation of aberrant proviruses. Host DNA is shown in bold blue and orange lines, and viral DNA is indicated by thin blue and orange lines. The shaded boxes in *A* indicate viral LTRs. (*A*) The normal end of the viral DNA is inserted by integrase (IN), whereas the aberrant end is not, and is presumably free to be inserted to the right or left of the original insertion, most likely by a host DNA polymerase-mediated copying/insertion reaction (*Discussion*) involving the defective 3′ viral end. (*B*) If the reaction involves host sequences to the left of the IN-mediated insertion event, and into the strand opposite the original 3′ insertion, the result is long direct repeats of the host sequence flanking the integrated viral DNA. (*C*) Copying/insertion of the defective 3′ viral end of the same strand as the original 3′ insertion results in inversion of the host sequences at the integration site. (*D*) Copying/insertion of the defective 3′ viral end to the right of the original insertion results in the deletion of host sequences at the site of integration.

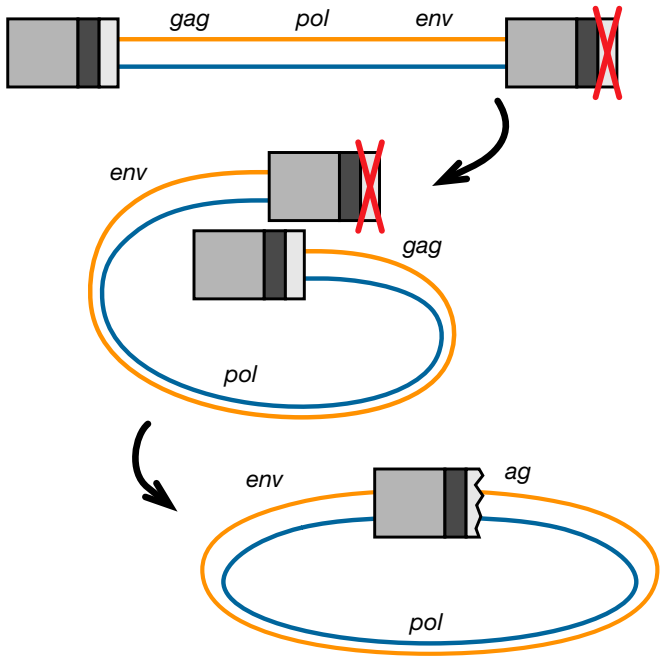

Fig. S4. Model for generation of aberrant circles. The presence of suboptimal concentrations of raltegravir could block the integration of one viral DNA end. As explained in *Discussion*, limited homology or microhomology of a blocked 3′ end could allow hybridization to some segment of the same viral DNA, which could result in copying of this segment, generating a homologous segment. This could serve as a substrate for homologous recombination, leading to the generation of a circular form of viral DNA. We suspect that a host DNA polymerase is involved in the copying/insertion reactions that generate these aberrant unintegrated circles. This is in contrast to the autointegrated circular viral DNAs, whose junctions do not involve microhomology, that are presumably generated by IN and are found in untreated cells.