Table 1. Processivity of DNA polymerases. Data from Kornberg and Baker [46] and as indicated. SV 40, simian virus 40; EBV, Epstein Barr virus; AMV, avian myeloblastosis virus; gp, gene product; pol, polymerase; n.d., not determined; −, not applicable.

Polymerase	Subunits		Processivity		Processivity device
	core	holoenzyme	core	holoenzyme	
E. coli pol III	3 (α, ε, θ)	≥10	10−15	>5000	β subunit sliding clamp
Phage T4 pol	1 (gp43)	4	11−13	>20000	gp45 sliding clamp
Yeast/human pol δ	1 (δ)	≥7	2	high	PCNA sliding clamp
SV 40 pol α	1 (α)	4	n.d.	high	PCNA sliding clamp
Phage T7 pol	1 (gp5)	2	50 [22]	>10000 [22]	*E. coli* thioredoxin host factor
E. coli pol II	−	1	−	5 [47]	n.d.
E. coli pol I	−	1	−	11−200 (DNA template), 3−4 (RNA template) [48]	n.d.
Human pol α	−	1	−	10 [49]	n.d.
Vaccinia virus pol	−	1	−	≥2000 [50]	n.d.
EBV pol	−	1	−	≥7200 [51]	n.d.
Phage T5 pol	−	1	−	155−170	n.d.
AMV pol	−	1	−	22−30	n.d.
HIV-1 RT	2 (p66/p51)	2 (p66/51)	5 (DNA template), 340 (RNA template) [32]	5, 340	n.d.

replicate long DNA templates, and these enzymes thus display a high degree of processivity. Polymerases needed for DNA repair show low processivity, since these enzymes need to synthesize only short stretches of nucleic acid. Processivity is realized in different systems quite differently. Some polymerases with very high processivity bind to accessory proteins that form closed circular clamps around the template DNA, thus preventing polymerase dissociation. The three-dimensional structures of two such sliding processivity clamps have been determined, namely the β subunit of *E. coli* polymerase III [19] and the proliferating-cell nuclear antigen (PCNA) that associates to polymerase δ in the human and yeast systems [20]. Although the structures and functions of these two clamp proteins are similar, they share no significant sequence identity [21]. The sliding clamps are found in eucaryotes, bacteria, and viruses (Table 1). The polymerase of bacteriophage T7 gains high processivity in DNA synthesis by recruiting the host protein thioredoxin, the processivity-promoting mechanism of which is unknown [22]. The variety of different mechanisms that enhance processivity suggests that these mechanisms have developed largely independently in the different polymerase systems, and emerged some time after development of the polymerase activity itself.

Processivity is closely linked to translocation when protein/nucleic-acid contacts are disrupted and re-established during polymerase movement. Therefore, any proposed mechanism for polymerase translocation needs to explain the observed processivity of the respective enzyme. There is a debate on how template-dependent nucleic acid polymerases move along their templates. It was suggested that contraction and extension of the substrate nucleic acid by a transition of the substrate nucleic acid from the A to B form contributes to polymerase translocation [12]. This model is plausible for polymerases with DNA substrates, because DNA can convert from the B form to the A form upon binding to proteins. We exclude the possibility of this model for HIV-1 RT, since this polymerase must accept substrate nucleic acids which are already in the A form such as RNA/DNA and RNA/RNA duplexes. For *E. coli* RNA polymerase, an inchworm-like movement of the protein was suggested [23, 24], assuming contraction and stretching of the polymerase. A ratchet-type mechanism was proposed for translocation of HIV-1 RT [25]. Inchworm and ratchet-type models are conceptually similar, as they require at least two binding sites for the template that act separately but in concert, indicating some kind of communication between the two sites. One of the binding sites must be flexible to follow the movement of the template relative to the polymerase active site. Both models apply to continuous or to discontinuous translocation. The translocation process is termed continuous if movement of the polymerase occurs after each step of synthesis, and is termed discontinuous if the movement occurs only after incorporation of several nucleotides. While recent studies on stalled transcription complexes of *E. coli* RNA polymerase indicate that translocation encompasses continuous and discontinuous steps, such as jumping of polymerase [26], a simple continuous translocation model is assumed to apply for HIV-1 RT. This model is suggested from footprinting data of HIV-1 RT arrested in specific registers of DNA synthesis, which show no changes in the protection pattern in the different registers [27].

In this study, we investigated HIV-1 RT. This enzyme has a prominent position among template-dependent nucleic acid polymerases, since its three-dimensional structure is known in detail from crystallographic analyses [10−12, 28]. This facilitates testing of models that explain RT translocation on a structural level. HIV-1 RT is a template-dependent DNA polymerase that catalyzes a key step during retroviral infection, namely the synthesis of a DNA copy of the viral RNA genome [29, 30]. During reverse transcription, RT has to accept RNA and DNA as a template [31]. The viral RNA is the template during minus (first)-strand DNA synthesis. This DNA serves as template during plus (second)-strand DNA synthesis. Processivity of RT is low and varies depending on whether RNA or DNA is used as a template. Reardon has shown [32] that around 340 nucleotides are incorporated/binding event in the RNA-dependent synthesis mode and only 5 nucleotides/binding event in the DNA-dependent mode.

Here we suggest a model for RT translocation which is based on two assumptions. (a) There are two template-binding sites, which are located in the two subunits of RT, in the thumb subdomains. We suggest that the helix-clamp motif, recently described as being conserved in different polymerases [18], is essentially responsible for interaction with the nucleic acid template. (b) The thumb subdomain in the p66 thumb is flexible, which provides a movable template-binding domain required for translocation. Flexibility of the thumb was suggested previously by inspection of HIV-1 RT models obtained by crystallographic studies [12, 28].