

Review

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Review

TARDBP as a Gatekeeper of HIV-1 Assembly and Infection: Targeting the Viral Capsid Precursor Pr55^{Gag} and Limiting Viral Core Entry

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Abstract

TARDBP (TDP-43), a multifunctional RNA-binding protein, has emerged as a critical host factor controlling HIV-1 replication by destabilizing the viral capsid protein (CA) 55 kDa Gag precursor (Pr55^{Gag}). TARDBP promotes HDAC6-mediated autophagic degradation of HIV-1 Pr55^{Gag} and Vif, impairing nascent virion assembly and infectivity. Simultaneously, TARDBP disrupts viral entry by modulating HDAC6-dependent microtubule (MT) deacetylation, blocking the viral core at the pore fusion step in target cells. These dual mechanisms position TARDBP as a central antiviral defender, paralleling the CA (viral core)-targeting activity of TRIM5α and novel therapeutic inhibitors such as lenacapavir. This review synthesizes evidence for TARDBP's roles in HIV-1 restriction, highlighting its potential to destabilize the CA-formed viral core during both viral assembly and entry. We propose that enhancing TARDBP activity, combined with destabilizing CA-binding drugs, could offer a synergistic strategy to combat drug-resistant HIV-1 strains and target viral reservoirs, providing hope for functional cure approaches.

Keywords: TARDBP (TDP-43); HIV; Pr55^{Gag} degradation; capsid (CA) and viral core; virus replication and infection; potential antiviral target

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) 55 kDa Gag precursor protein (Pr55^{Gag}) mediates viral core formation (i.e., by assembling the capsid protein (CA) [1–3]) and budding which makes it essential for viral replication ([2,4,5], reviewed in [6]). While antiretrovirals mainly target later stages of the viral life cycle (e.g., integrase, protease) [7,8], vulnerabilities in CA-viral core formation had remained underexplored until the use of the next-gen CA inhibitor lenacapavir [8–10]. This new drug selectively binds to the hexamer subunits of the HIV-1 CA protein, disrupting the viral core lattice and impairing both the nuclear import of viral DNA and viral CA generation [11–16], thereby acting at the early and late stages of the HIV life cycle.

Host proteins such as tripartite motif-containing protein 5 alpha (TRIM5 α) exemplify the innate CA-targeted restriction of retroviruses. Briefly, the mechanism of TRIM5 α -mediated retroviral restriction involves a multistep process initiated by the multivalent binding of TRIM5 α to the incoming viral capsid lattice, which can induce premature disassembly, or uncoating, and directly inactivate HIV-1 and other retroviral cores [17]. This binding event, while potentially disruptive on its own [18–22], is significantly enhanced by the E3 ubiquitin ligase activity of the Really Interesting New Gene (RING) finger domain, which promotes self-ubiquitination and recruits the ubiquitin–proteasome system to accelerate nonproductive uncoating and degrade core components [20,23–29]. In fact, HIV-1 can evade the host's innate immune response by using its viral core to conceal its nucleic acids from detection. Thus, when the HIV-1 CA carries mutations that disrupt its interactions with host proteins, this evasion fails [30]. These viral cores bearing CA mutants may also alter viral trafficking within the cell, leading to premature reverse transcription; this exposes the viral DNA to host-cell sensors, which then triggers a signaling pathway involving the transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and interferon regulatory factor 3 (IRF3) to induce type 1 interferon (IFN) production [30]. The role of the proteasome in accelerating TRIM5 α -mediated restriction appears to be secondary, as TRIM5 α binding alone can divert the core into an off-pathway trajectory that disables infectivity even when reverse transcription proceeds [27,31–33]. On the other hand, TRIM5 α could activate autophagy effectors (called virophagy), although this pathway seems redundant for nuclear inactivation. [34–38].

Recent work identified transactive response DNA-binding protein (TARDBP), also known as transactive response DNA binding protein 43 kDa (TDP-43), as a novel regulator of Pr55^{Gag} stability [39,40]. TARDBP, best known for its role in neurodegenerative diseases (reviewed in [41]), unexpectedly suppresses HIV-1 by degrading Pr55^{Gag} and limiting its incorporation into nascent virions thus hampering viral production, [39] and possibly disrupting subsequent capsid maturation. Moreover, TARDBP establishes the permissive status of cells infected by HIV-1 through the regulation of the histone deacetylase enzyme 6 (HDAC6) mRNA and protein expression levels, which restricts HIV-1 entry by its microtubule (MT) deacetylation activity [40]. In fact, TARDBP is a nuclear RNA-binding protein able to process RNA, acting on transcription splicing, mRNA transport, stability and translation, and pri-miRNA processing [42–50]. TARDBP recognizes UG-rich mRNA sequences [45,46,51] and can therefore influence the processing of hundreds to thousands of transcripts, including the one coding for the cytoplasmic enzyme HDAC6 (i.e., one of the transcripts that is mainly regulated by TARDBP) [40,52]. Notably, HDAC6 promotes the deacetylation of the α -tubulin subunit in MTs, modulating cytoskeleton dynamics [40,53–61] and pore fusion formation during the first steps of the HIV-1 infection process [55,57,58], thereby affecting the infection activity of the HIV-1 envelope glycoprotein complex (Env) [40,55,56,62]. Therefore, TARDBP regulates infection by acting at the early and late stages of the HIV-1 life cycle.

This review explores TARDBP's dual antiviral mechanisms, highlights its potential alongside lenacapavir which was approved by the Food and Drug Administration (FDA) in 2022 for clinical use in combination with other antiretroviral(s) in heavily treatment-experienced HIV-1 patients with multidrug-resistance (reviewed in [63]), and proposes strategies to harness TARDBP for clinical intervention.

2. TARDBP Regulating Virion Formation and Infectiveness

A sentinel Against Pr55^{Gag} Correct Processing and Virion Incompetence

TARDBP is a nuclear RNA-binding protein that performs crucial biological tasks in cells, such as splicing, transcription and translation; mRNA transport; mRNA stability; and pri-miRNA processing [40,42–49,51,64]. TARDBP is able to interact with hundreds to thousands of transcripts, including the proautophagic and anti-HIV-1 factor HDAC6-tubulin deacetylase enzyme, which is highly regulated by TARDBP [39,40,52]. The level of expression of the TARDBP protein directly affects the mRNA and protein levels of HDAC6, which has been previously reported to control

Pr55^{Gag} stability and the expression of the auxiliary viral infectivity factor (Vif) protein of HIV-1 [65]. It is thought that HIV-1 uses Vif in combination with the protein core binding factor β (CBF- β) to promote the degradation of the host restriction factor apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3G (APOBEC3G or A3G) [66–68], thereby increasing viral infectivity. Notably, cellular HDAC6 counteracts this viral strategy by forming a complex with A3G, which stabilizes A3G by competing with Vif for binding [65]. HDAC6 directly interacts with Vif itself via its C-terminal binder of ubiquitin zinc finger (BUZ) domain [65] (also known as the zinc-finger ubiquitin-binding (ZnF-UBP) or the polyubiquitin-associated zinc finger (PAZ) domain) [69–71] and, in a process requiring its deacetylase activity, promotes the autophagic degradation of Vif without affecting its CBF- β partner [65]. This dual action of HDAC6, which stabilizes A3G and degrades Vif, antagonizes the proviral Vif/CBF- β complex, reduces the amount of Vif incorporated into new virions, and consequently diminishes HIV-1 infectivity. Furthermore, HDAC6 acts against HIV-1 infection in a later step of the viral cycle. HDAC6 limits viral production and infection by promoting the aggresome/autophagic degradation of the viral polyprotein Pr55^{Gag} [65,72], an effect independent of the presence of A3G in virions, thus identifying a new HDAC6/A3G cellular complex involved in antiviral defense [65] by targeting Vif and the CA precursor, the polyprotein Pr55^{Gag}, for autophagy degradation [65,72].

As for other restriction factors, HIV-1 counteracts the antiviral activity of HDAC6 using the negative regulatory factor (Nef) of HIV-1 [72]. Nef induces HDAC6 degradation through an acidic/endosomal-lysosomal process, which is mediated by its polyproline-rich region (P72xxP75, aa 69-77) and a di-leucine motif (ExxxLL160-165). By degrading HDAC6, Nef stabilizes the Pr55^{Gag} and Vif viral proteins, ensures the proper localization and aggregation of Pr55^{Gag} at the plasma membrane for viral egress, and ultimately enhances the infectivity of viral particles [72]. This interplay between HIV-1 Nef and cellular HDAC6 could be a key determinant of viral infection and pathogenesis, indicating that both molecules are critical therapeutic targets for combating HIV-1.

Similarly, TARDBP and the TARDBP/HDAC6 axis have been reported to control HIV-1 infection [39]. We suggest that TARDBP functions as a key cellular regulator of the late stages of the HIV-1 viral cycle by stabilizing the anti-HIV-1 factor HDAC6. The overexpression of TARDBP in virus-producing cells increases HDAC6 levels, which in turn triggers the autophagic degradation of the CA precursor, the viral protein Pr55^{Gag}, together with HIV-1 Vif, thereby inhibiting viral particle production and reducing virion infectivity by limiting the incorporation of these proteins into new particles [39].

Conversely, TARDBP knockdown reduces HDAC6 expression, increases the stability of HIV-1 Vif and Pr55^{Gag}, and enhances both virion production and infectious capacity (**Figure 1**, *summary of the TARDBP presented data*).

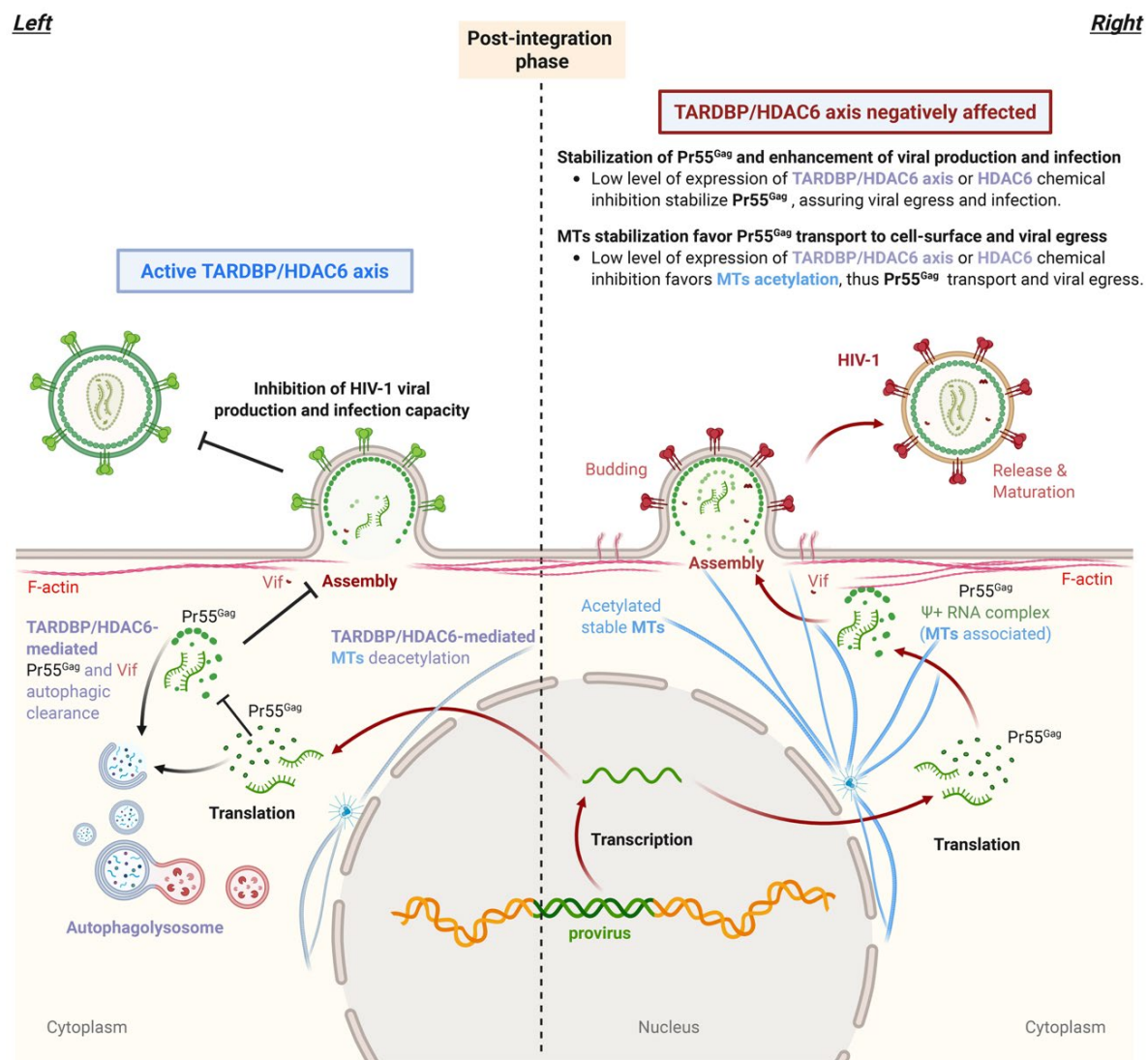


Figure 1. Scheme illustrating the functional role of TARDBP in late stages of the HIV-1 life cycle. *Left*, the increase in TARDBP activity enhances the action of the autophagic HDAC6 enzyme (i.e., by first stabilizing the HDAC6 mRNA levels; not shown on the illustration), thereby targeting HIV-1 Pr55^{Gag} for autophagic degradation together with the viral Vif protein. The scheme shows that the transcription and translation of the integrated HIV-1 genome generate viral RNA⁺ and proteins, with the structural Pr55^{Gag} polyprotein being relevant for recognizing viral RNA⁺ and recruiting a complex to stable MTs to travel to the plasma membrane; however, under these conditions, Pr55^{Gag} is degraded, limiting virus assembly, budding and egress. Similarly, the MT-associated HDAC6 enzyme deacetylates stable MTs, impeding Pr55^{Gag} cell-surface localization. *Right*, in contrast, TARDBP silencing (low levels of the cellular protein) or chemical inhibition of HDAC6 favors the stabilization of the Pr55^{Gag} and Vif proteins, together with the acetylation of MTs, thereby promoting the trafficking of the HIV-1 Pr55^{Gag} MT-dependent cellular machinery to the cell surface, where it assembles and buds to form viral particles that incorporate Vif (red dots; which are not shown in virions on the *left panel*-virus scheme)) to ensure the infectivity of nascent HIV-1. Designs and templates were created with BioRender and licensed are obtained for publication.

In turn, TARDBP knockdown that diminishes the level of expression of the HDAC6 enzyme or HDAC6-tubulin deacetylase chemical inhibition promotes stabilization of acetylated MTs [39,40,57], which favors Pr55^{Gag} association with MTs and its transport to plasma membrane where Pr55^{Gag} orchestrates virus budding and egress of infectious viral particles (reviewed in [73]).

The inability of a nuclear localization signal (NLS)-TARDBP mutant to control HIV-1 confirmed the functional importance of this pathway. These findings establish the TARDBP /HDAC6 axis as a

critical cellular mechanism for controlling HIV-1 production and infectiveness, with a direct relationship observed between the virion content of Vif and the CA precursor Pr55^{Gag} and the resulting infection capacity [39].

3. TARDBP at the Portal

Blocking Viral Core Entry and Early Infection via HDAC6 Regulation

The second arm of TARDBP's antiviral activity involves disrupting viral entry and early steps of infection [40]. TARDBP shapes CD4⁺ T-cell permissivity to HIV-1 infection by regulating HDAC6-tubulin deacetylase levels. HDAC6 deacetylates MTs at the Lys⁶⁰ residue of the α -tubulin subunit [53,57], destabilizing MT networks and impairing pore fusion formation and HIV-1 infection [40,57]. In fact, the acetylation of MTs is a cytoskeleton event required to facilitate HIV-1 envelope (Env)-mediated membrane fusion, subsequent viral core entry and infection of target cells [57]. Therefore, HDAC6-tubulin deacetylase activity prevents CA-associated viral core entry and infection. In this context, overexpression of TARDBP stabilizes the mRNA of HDAC6 and increases the level of expression of the enzyme, which impairs HIV-1 infection by reducing the fusion capacity of the viral Env glycoprotein complex (i.e., formed by trimers of the noncovalently associated gp41/gp120 (glycoprotein 120) viral Env proteins (reviewed in [74,75])). Likewise, this effect is independent of HIV-1 Env tropism [40]. Conversely, silencing endogenous TARDBP decreases HDAC6 and increases HIV-1 Env-mediated fusion and infection, a process that is directly dependent on Env/CD4-mediated stabilization of acetylated MTs [40,55–58,62]. This regulatory mechanism of TARDBP and the TARDBP/HDAC6 axis was confirmed by analyzing the function of HIV-1 Envs from viruses isolated from patients with different disease progression and clinical outcomes.

Thus, activation of the TARDBP/HDAC6 axis reduces infection of virus-bearing functional Envs from virus of viremic nonprogressor (VNP) and rapid progressor (RP) patients [40] to low levels observed with virions bearing non-functional Envs from virus of long-term nonprogressor elite controller (LTNP-EC) individuals [40]. In contrast, silencing of the TARDBP/HDAC6 axis enhances the infectivity of all primary HIV-1 Envs, including those deficient in function isolated from viruses of LTNP-ECs [40].

Thus, TARDBP controls HDAC6-tubulin deacetylase activity, regulating virus-cell membrane fusion and subsequent CA-associated viral core entry, thereby conditioning cell permissivity to HIV-1 infection (Figure 2, summarizes these TARDBP presented data).

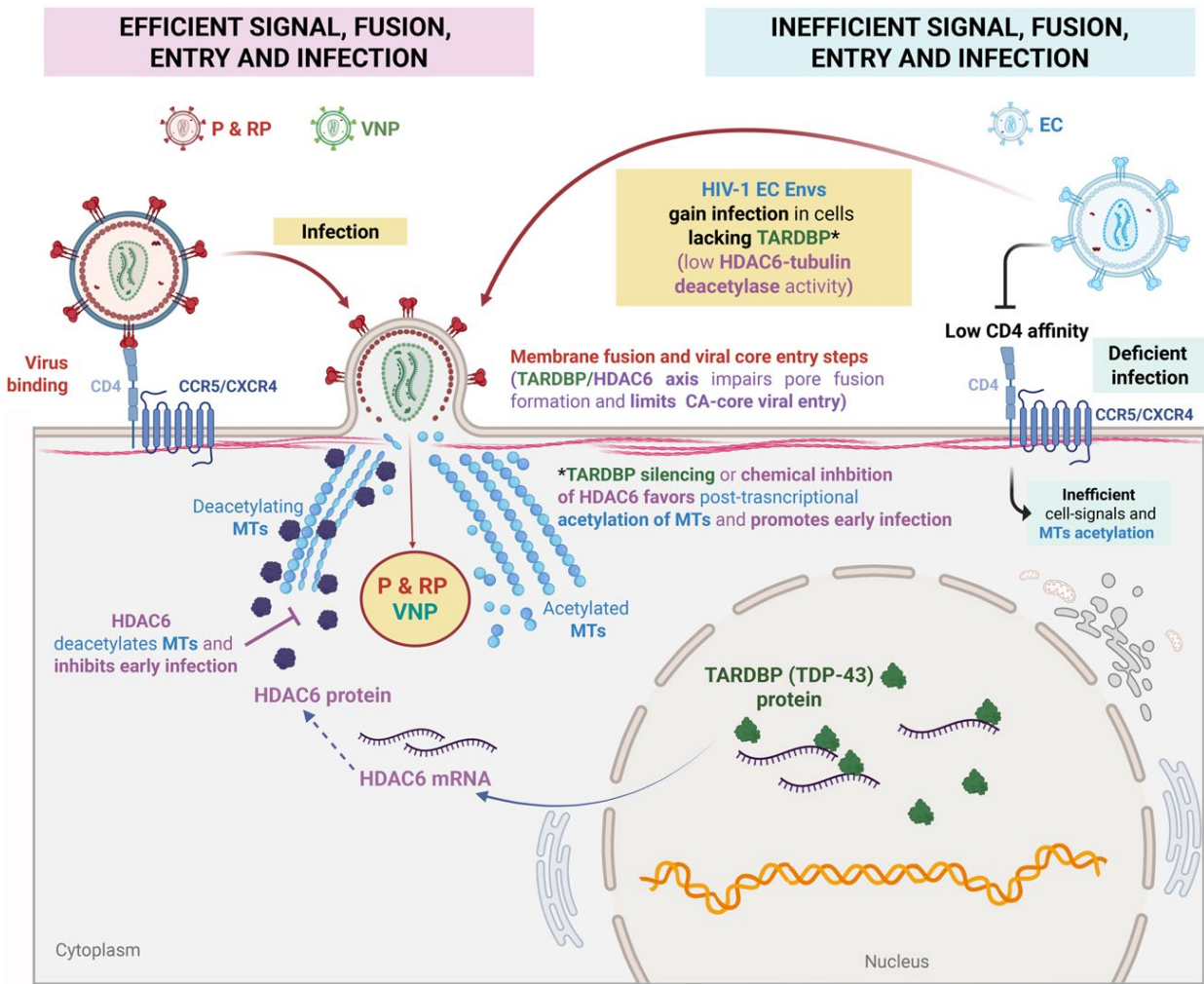


Figure 2. Scheme illustrating the functional role of TARDBP in the early stages of HIV-1 infection. Functional HIV-1 Envs from progressors, (P) rapid progressors (RP) and viremic nonprogressors (VNP) patients trigger MT acetylation in a CD4-dependent manner to promote pore fusion and evade the antiviral action of the endogenous tubulin-deacetylase HDAC6, which is under the control of TARDBP (TDP-43). Thus, activation of the TARDBP/HDAC6 axis by overexpressing TARDBP, stabilizes HDAC6 mRNA and increases HDAC6-tubulin deacetylase enzyme activity, inhibiting HIV-1-mediated pore fusion formation, viral core entry and early infection. Functional HIV-1 Env complexes, such as those from viruses of P, RP and VNP patients, are able to stabilize acetylated MTs, overcoming the endogenous activity of TARDBP and the antiviral TARDBP/HDAC6 axis. In this sense, deficient HIV-1 Envs from viruses of long-term nonprogressor Elite Controller (LTNP-EC) individuals are insufficient to form the fusion pore and infect because of their inability to escape the antiviral TARDBP/HDAC6-tubulin-deacetylase barrier. Notably, viral particles bearing EC-Envs gain infection function when HDAC6 or the HDAC6/TARDBP axis is inhibited by either HDAC6 inhibitors or their nonactive mutants or interference with HDAC6/TARDBP mRNA, thereby stabilizing MTs to generate a permissive state for infection. Designs and templates were created with BioRender and licensed are obtained for publication.

Taken together, these findings suggest that TARDBP could be relevant for the pathogenesis of HIV-1 infection, as recent works indicate that the infective properties of the HIV-1 Env complex of viruses from infected individuals are directly related to different infection progression rates in vivo [40,55,56,62]. Thus, CD4 binding, fusion and cell-to-cell viral transfer, and the cell-signal capacities of the HIV-1 Env complex affect the infectivity of HIV-1 [40,55–57,62], which is under the control of the endogenous TARDBP/HDAC6 axis. Likewise, nonfunctional LTNP-EC Envs are unable to overcome this barrier and stabilize acetylated MTs to efficiently trigger pore fusion, and only functional viral

Env complexes from patients with detectable viremia (i.e., VNPs, Ps and RPs) are efficient by stabilizing acetylated MTs against the endogenous TARDBP/HDAC6 axis [40].

4. Perspective

TARDBP as a Potential Clinical Target

Besides the well-defined role of TARDBP in the HIV life cycle, an imbalance in the expression and function of TARDBP and HDAC6 has been associated with neurodegeneration and disease in the central nervous system (CNS) [76–83]. In addition, HDAC6 has been shown to protect against neurotoxicity induced by the HIV-1 Env subunit gp120 in cortical neurons [84]. These findings suggest that the activation of TARDBP (i.e., gene/protein expression and/or protein stability) and/or the TARDBP/HDAC6 axis may play a protective role against HIV-1-mediated toxicity in the CNS. Conversely, dysregulation of their expression and function could exacerbate HIV-1-induced damages, a hypothesis that requires further investigation. Nevertheless, HDAC6 inhibitors (e.g., the potent and selective inhibitor tubastatin A and the nonspecific trichostatin A (TSA) inhibitor [57,58,85]) enhance cell permissivity to HIV-1 infection and trigger HIV-1 transcription [57,58,86], suggesting that TARDBP acts as a natural HDAC6 agonist, as indicated by the anti-HIV-1 activities of the TARDBP/HDAC6 axis [39,40] (**Figures 1 and 2**). Among the mechanisms involved in this effect, autophagy promotion is a key antiviral function of the TARDBP/HDAC6 axis. Considering the relevance of autophagy in HIV-1 infection (reviewed in [87]), it could be of interest to develop new drugs and anti-HIV-1 strategies at that level.

In particular, TARDBP could be considered a potential target against HIV-1 [39,40], considering the potential side effects of drugs and/or treatments on the CNS and immune system (reviewed in [88]). Thus, the clinical translation of screening-based compounds that could enhance TARDBP-mediated targeting and clearance of HIV-1 Pr55^{Gag} could be considered to avoid CA-associated viral core formation and, therefore, impairing virus production and HIV-1 spread in reservoirs and the organisms. It is conceivable that these TARDBP-boosting agents (i.e., activating selective drugs for gene expression or stabilizing the protein) could act in a similar fashion as lenacapavir (Sunlenca®), a new anti-HIV drug that targets the CA lattice that constitutes the viral core of HIV [8–16]. As reported for TARDBP, lenacapavir inhibits viral replication at both the early and late stages of the HIV-1 life cycle. On 22 August 2022, lenacapavir was approved in the EU for use in combination with other antiretroviral(s) in adults with multidrug-resistant HIV-1 infection, for whom it is otherwise not possible to construct a suppressive antiviral regimen ([8–16], reviewed in [63]).

Therefore, recent advances in viral core/CA inhibitors, such as lenacapavir, which stabilizes capsid intermediates to block nuclear import, may synergize with TARDBP-enhancing therapies. For example, lenacapavir's "hyperstable capsid" phenotype might render HIV-1 more susceptible to TARDBP-mediated HIV-1 Pr55^{Gag} degradation in infected, virus-producing cells, creating a potential two-pronged attack in combination trials.

5. Conclusions

TARDBP has dual roles in HIV-1 restriction, limiting **i**) virus production and infectivity and **ii**) viral entry and infection by targeting Pr55^{Gag}, positioning it as a master regulator of CA-induced vulnerability of the viral core. By integrating its mechanisms with emerging CA inhibitors such as lenacapavir, researchers could pioneer therapies that overcome drug resistance. However, considering TARDBP's neuroprotective-antiviral duality, any anti-HIV-1 strategy will require innovative delivery systems (e.g., targeted nanocarriers) to selectively act on anatomical, cellular and molecular HIV-1 reservoirs (reviewed in [89]) to avoid undesirable side effects on the CNS. As the field revisits CA (viral core)-centric strategies, TARDBP has emerged as a potential target for new HIV-1 therapeutics for functional cure approaches.

Abbreviations

APOBEC3G (or A3G), *cytidine deaminase restriction factor apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3G*
BUZ domain, *binder of ubiquitin zinc finger*
CA, *capsid protein*
CBF-β, *core binding factor β*
Env, *envelope (HIV envelope glycoproteins complex)*
FDA, *Food and Drug Administration*
gp41, *glycoprotein 41 (of the HIV-1 Env complex)*
gp120, *glycoprotein 120 (of the HIV-1 Env complex)*
HDAC6, *histone deacetylase enzyme 6*
HIV-1, *human immunodeficiency virus type 1*
IFN, *interferon*
IRF3, *interferon regulatory factor 3*
LTNP-EC, *long-term nonprogressor elite controller (HIV individuals)*
mRNA, *messenger ribonucleic acid*
MT, *microtubule*
Nef, *negative regulatory factor (of HIV)*
NF-κB, *nuclear factor kappa-light-chain-enhancer of activated B cells*
NLS, *nuclear localization signal*
PAZ, *polyubiquitin-associated zinc finger*
Pr55^{Gag}, *55 kDa Gag precursor protein (of HIV)*
Ps, *progresors (HIV patients)*
RING, *Really Interesting New Gene (it is a finger domain)*
RPs; *rapid progressors (HIV patients)*
TARDBP, *transactive response DNA-binding protein*
TDP-43, *transactive response DNA binding protein 43 kDa*
TRIM5α, *tripartite motif-containing protein 5 alpha*
TSA, *trichostatin A*
Vif, *viral infectivity factor*
VNPs, *viremic nonprogressors (HIV patients)*
ZnF-UBP, *the zinc-finger ubiquitin-binding domain*

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