Purpose of review
The present review will discuss recent advances in the development of anti-HIV therapies inspired by studies of the mechanisms of host restriction factor-mediated resistance to HIV infection.

Recent findings
Manipulating the interplay between host cell restriction factors and viral accessory factors that overcome them can potentially be therapeutically useful. Preliminary successful therapies – some of which are entering clinical trials – either inhibit the ability of virus to evade restriction factor-mediated immunity, or promote intracellular levels of restriction factors. These aims are achieved by multiple means, which are discussed.

Summary
Many restriction factors appear to provide potentially useful targets for anti-HIV therapies, so time and interest should be invested in investigating ways to successfully therapeutically manipulate restriction factor-mediated immunity.

Keywords
anti-HIV therapies, HIV, host-mediated immunity, restriction factors

INTRODUCTION
In the present year the United Nations General Assembly in its ‘Political Declaration on Ending AIDS’ agreed to a momentous plan to fast track ending the AIDS epidemic by 2030. Such optimism arose from the success of highly active antiretroviral therapy (nowadays referred to simply as ART), which controls HIV-1 replication in vivo over decades, preventing progression to AIDS and thereby maintaining HIV infection as a chronic, manageable medical condition [1].

Drugs that target HIV-1 have been developed to every characterized step in the viral life cycle [2,3]. A class of drugs composed of fusion inhibitors and CCR5 antagonists act at the initial binding to cellular receptors CD4 and a chemokine receptor, either CCR5 or CXCR4, to prevent fusion with the cell membrane [3,4]. Reverse transcription is initiated after fusion with the plasma membrane and is inhibited by two classes of drugs: nonnucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors. Integrase catalyses the insertion of the newly synthesized double-stranded viral cDNA into the host cell DNA. This final step in the early stage of the life cycle is inhibited by integrase strand transfer inhibitors. In addition to these early targets, protease cleaves Gag and Gag-Pol during particle release from the infected cell and this process is blocked by protease inhibitors [2].

Despite the enormous progress in the development and, equally importantly, the distribution of such drugs globally, the consensus at the recent International AIDS conference in Durban, South Africa (2016) was that we must ‘reject complacency’. UNAIDS says that the decline in new infections in adults has stalled with significant increases in the number of new infections – especially in East Europe, Asia, the Middle East and North Africa. Worldwide nearly 2 million people became infected last year. Hobbs et al. observe viral resistance in treatment-naïve patients [5], whereas Medicines San Frontières, who monitor drug resistance in Africa, have found 10% resistance. Clearly, in the absence of a vaccine, innovative therapeutic options are imperative for the future management of HIV-1 infection.

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Curr Opin Infect Dis 2016, 29:609–614
DOI:10.1097/QCO.0000000000000322
Antimicrobial agents: viral

KEY POINTS

- Various interventions aimed at manipulating the interactions between host cell restriction factors and viral accessory factors are being investigated as potential anti-HIV therapies.
- Gene therapies involving ex-vivo cell modification using lentiviral vectors expressing anti-HIV-1 genes that are related to restriction factors have had some success, but are unlikely to provide an ultimate solution for currently infected individuals.
- Novel therapeutic options are urgently required in the ongoing battle to manage and even cure HIV-1 infection.

In recent years it has become evident that host cells have their own battery of antiviral factors known as restriction factors which patrol the cell to protect against pathogen invasion (Table 1). The early steps in the HIV life cycle are targeted. Although such factors are often activated by interferon (IFN), they are intrinsically expressed in the host cell [6,7]. Restriction factors, therefore, can act even before the IFN response is triggered. In response to this onslaught, HIV has evolved various mechanisms that mitigate restriction factor inhibition [6,8].

Most, though not all, restriction factors act in the early phase of the replication cycle prior to proviral integration. Two well characterized factors act during reverse transcription. Apolipoprotein B mRNA editing enzyme-catalytic polypeptide-like 3s (APOBEC3 G/F) are cytidine deaminases that are loaded into the virus particle during assembly. They operate in the next target cell in which viral cDNA synthesis is inhibited by inducing inactivating G-to-A hypermutations in the reverse-transcribed genome [9–11]. Sterile alpha motif and HD-containing protein 1 (SAMHD1) inhibits retroviral reverse transcription in monocytes, macrophages, dendritic and resting T cells by sequestering cellular dNTPs [12–15]. After reverse transcription Myxovirus resistance 2 (MX2) inhibits the nuclear entry of the proviral cDNA [16–18]. At the late post-integration stages of replication Tetherin prevents virions from budding from the plasma membrane during assembly [19] whereas SERINC5 and SERINC3 render HIV and SIV particles less infectious [20,21]. A variety of additional antiviral factors, such as IFITM proteins, CH25H, KAP1/TRIM28, 90K, MOV10, SLFN11, ZAP, and REAF have been described [7,22]. The present review will focus on early restriction factors that are currently being pursued as therapeutic candidates.

DISARMING THE VIRUS

In addition to gag, pol, and env genes, HIV has the so-called accessory genes: vif, vpu, nef, and vpr/vpx [23**,24]. The function of these accessory genes in viral replication is to protect the virus from the antiviral effects of cellular restrictions (Table 1) [7]. Vif mitigates APOBEC3 whereas Vpx, produced by HIV-2 and SIV isolates, abates SAMHD1 [6,24,25]. Interestingly HIV-1, for unknown reasons, does not encode a vpx gene and remains susceptible to SAMHD1. In the post-integration late stage of replication, Vpu mitigates the effects of Tetherin whereas Nef prevents SERINCs from being loaded onto viral particles [20,21].

Viral accessory proteins represent a logical target for intervention and their inhibition would clear the way for host defences to reestablish dominance. Vif counterattacks APOBEC3G, the most potent APOBEC, by mediating its proteosomal degradation, preventing its inclusion into viral particles [26,27]. Disrupting Vif–APOBEC3G interactions inhibits HIV replication in vitro [28]. MLN4924, an antiviral compound currently in phase I clinical trials, inhibits the NEDD8 cascade which is required upstream of the pathways leading to proteasome degradation including that used by Vif to degrade APOBECs. Thus, MLN4924 prevents Vif activation of the E3 Ubiquitin Ligase Complex, stopping HIV-1 from circumventing APOBEC3G restriction [29]. MLN4924 inhibition of neddylation also prevents Vpx-mediated SAMHD1 proteosomal degradation [30]. Considering the crucial role of proteasomal degradation in the control of protein expression in maintaining healthy cells in vivo, further development will need to focus more specifically on direct interactions. To this end, Nathans et al. [31] developed a high-throughput screen to identify direct

| Table 1. Host restriction factors, corresponding viral accessory factors, and the drugs by which they are targeted |
|---------------------------------------------------------------|
| Restriction factor | Accessory factor | Corresponding drugs |
|-------------------|-----------------|---------------------|
| APOBEC3G [23**]   | Vif [25]        | IMB26 [32]          |
|                   |                 | IMB35 [32]          |
|                   |                 | MLN4924 [29]        |
|                   |                 | RN-18 [31]          |
| SAMHD1 [23**]     | Vpx [24]        | MLN4924 [30]        |
| [Unknown] [23**]  | Vpr [23**]      | Damancanthal [55]   |
|                   |                 | Fumagillin [53]     |
|                   |                 | Vipirin [54]        |

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antagonists of the Vif–APOBEC interaction. RN-18, identified as specific to the Vif–APOBEC interaction, increases cellular levels of APOBEC and its subsequent incorporation by virus. This offsets the potential side effect of inhibiting ‘normal’ cellular protein degradation. A second screen by Cen et al. [32] identified IMB26 and IMB35, which also specifically prevent the degradation of APOBEC3G.

Further development of drugs that target the APOBEC3G–Vif or SAMHD1–Vpx interactions will ideally continue to focus on precise targeting for greater specificity. Understanding the detailed structural determinants will be key in this [33,34] and will be assisted by the recent elucidation of detailed crystal structures of specific binding domains [35,36].

The use of Vif–APOBEC antagonists may, however, be problematic because of their potential to amplify the variability of HIV. Enhancing the pool of genetic variants in patients already on ART could enhance the generation of drug resistant variants [37**,38]. Indeed, in-vitro studies examining the emergence of resistance to reverse transcriptase suggest this is a real possibility [39,40]. It will be important to fully assess their suitability for treatment in the presence of current drug therapies.

**VPR ‘THE ORPHAN’ ACCESSORY PROTEIN**

Vpr accessory protein is crucial for HIV-1 replication in primary macrophages *in vitro* [10]. The precise role of Vpr, however, has been obscure since its discovery more than 25 years ago [41]. Its importance in early infection is reflected in that, like Vpx, it is highly conserved and is carried in significant amounts into viral particles [42] through a direct binding with p6 in Gag polyprotein during assembly [43,44]. It is released from the capsid shortly after viral entry [45] and it is widely speculated that, similar to Vpx, it has a role early in infection to counter-act an unknown restriction factor [10]. Experimental infections of rhesus macaques with SIVmac deleted for vpr have lower viral loads and delayed disease progression [46,47]. It is difficult to assess its role is pathogenesis in humans because it is highly conserved. Nonetheless two polymorphisms, R77Q and Q3R are overrepresented in individuals who progress very slowly to disease. The same mutations exhibit poor viral replication kinetics *in vitro* [48–51].

Vpr is known to induce G2 cell-cycle arrest, apoptosis and long terminal repeat transactivation of the integrated provirus [10,52]. Therapies aimed at interfering with these activities may offer effective targets. Some promising moves in this direction include the discovery of fumagillin that inhibits the effects of Vpr on the cell cycle [53]. The same group, Ong et al. [54] screened a chemical library and identified a 3-phenyl-coumarin based compound that inhibited the cell-cycle arrest activity and the Vpr-dependent infection of macrophages. Kamata et al. [55] described the identification of damnacanthal that specifically inhibits Vpr induced cell death but has no effect on G2 arrest.

Because vpr is so highly conserved it is reasonable to conclude that it is vital to HIV replication and may well, therefore, be an ideal target for antiviral therapy. A fundamental step in developing such a therapy will be to identify its target for proteasomal degradation, which indeed may be a novel restriction factor.

**MIMICKING RESTRICTION FACTOR ACTIVITY**

TRIM5a (tripartite motif 5-a) proteins were originally discovered as important determinants of the resistance of monkey cells to HIV-1 infection [56]. They bind to incoming viral capsids in the cytoplasm and lead to their rapid uncoating resulting in fewer reverse transcripts [56–58]. Recognition of the capsid by TRIM5 also activates an innate immune response against the virus [59]. Unlike other restriction factors, the activity of TRIM5 is not antagonized by an accessory gene. Instead, HIV-1 had evolved its capsid to avoid recognition by human TRIM5. But it is still susceptible to the Rhesus Monkey version [60,61]. Studies of the mechanism of rhesus TRIM5 inactivation of HIV have revealed that the stability of the HIV-1 capsid core is crucial to successful replication [58,62]. Developing small molecule drugs to mimic TRIM5a action has led to the discovery of PF74. PF74 inhibits HIV-1 infection by destabilizing viral capsid, leading to its premature disassembly that thwarts reverse transcription [63]. The replication of a resistant mutant to PF74 is weak in activated primary CD4⁺ T cells and macrophages suggesting that the routes for evolving resistance are limited. Several amino acid changes in the capsid (CA) protein are required [64].

Evidence continues to mount that the capsid needs to remain intact as it makes its way through the cytoplasm to the nucleus [65,66]. It is now thought that reverse transcription occurs within the capsid. The intact capsid could protect important viral components including reverse transcripts preventing them from direct recognition by antiviral factors or nucleic acid sensing receptors such as TREX and cGAS and consequently from triggering IFN [67,68].

Further protection may be gained from cellular cofactors such as cyclophilin A which binds to
incoming HIV-1 capsids and, in some circumstances, protects the virus from recognition by antiviral factors and by innate sensing [67]. The interaction with cyclophilin A is inhibited by cyclosporine. However, cyclosporine is immunosuppressive and would not be suitable for HIV therapy. A promising nonimmunosuppressive analogue of cyclosporine, SmBz-CsA which prevents protective masking of the capsid core by cellular cofactors, may be a promising alternative [67]. However, phase I clinical trials of alisporivir, a cyclophilin inhibitor derived from cyclosporine, found the drug had only a limited ability to reduce HIV-1 viral load [69].

If reverse transcription occurs within the intact capsid, a puzzle prevails as to how dNTPs, required for reverse transcription, could gain access. The assembled capsid core is formed from hundreds of CA protein hexamers and 12 CA pentamers [70–74] but with no obvious opening for access to dNTPs. The problem was recently solved by Jacques et al. [75] who describe an opening in each capsid hexamer bound by a ring of positively charged arginines and an amino terminal flexible β-hairpin termed ‘a molecular iris’. The ‘molecular iris’ could represent an excellent specific target for new therapeutic compounds. Indeed, the same group described a channel inhibitor, hexacarboxybenzene, proving the concept [75].

**GENE THERAPIES**

In 2008, an HIV-1-infected individual, later termed the ‘Berlin Patient’, was functionally cured of the virus after receiving a bone marrow transplantation from an individual with natural resistance to HIV infection [76]. The bone marrow donor was homozygous for a 32 base-pair deletion in the coreceptor gene CCR5 (CCR5-Δ32) which results in the loss of CCR5 expression at the cell surface [77]. This CCR5 mutation provides homozygous individuals with almost complete protection against HIV-1 infection, and heterozygous individuals with partial protection [77]. Despite this promising case, bone marrow transplantation from resistant individuals is not a plausible solution to the HIV pandemic on a global scale, due both to the inherent risks of the procedure and the low prevalence of the mutation among the general population. The case does, however, suggest that gene therapies following similar principles may be promising. Host restriction factors could present targets for such therapies. Many investigated therapies explore the effects of using gene therapy to either overexpress restriction factors in host immune cells, or express restriction factor variants that are resistant to HIV-1 accessory factors.

Gene therapies involving ex-vivo cell modification using lentiviral vectors expressing anti-HIV-1 genes that are related to restriction factors are certainly promising, and have had some success, even reaching clinical trials. A system involving the delivery of an antisense gene targeting the HIV-1 env gene is currently in clinical trials [78], whereas it has recently been reported that the delivery of a CRISPR-associated protein 9 (Cas9) targeting expression of the human coreceptor CCR5 expression at the genomic level confers resistance to R5-tropic HIV-1 [79].

Gene therapies which promote expression of the restriction factor APOBEC3G have also been proposed to improve immune resistance to HIV [80]. With mathematical models predicting that if a high proportion of CD4+ T cells overexpress APOBEC3G, HIV replication would be blocked *in vivo* [29].

Fusions of human and rhesus TRIM5α proteins that confer potent resistance are being considered for gene therapy. So far some success has been achieved in mouse models. CD34+ cells transduced with vectors expressing human–rhesus fusion TRIM5α successfully differentiated into thymocytes and were resistant to HIV infection [81].

TRIM5CypA is a TRIM5α–cyclophilin A fusion protein found naturally in owl monkeys. As with rhesus TRIM5α, TRIM5CypA has retained its ability to restrict HIV replication. Delivery of human mimics of TRIM5CypA by a lentiviral vector into human cell lines confers a resistance to HIV-1 infection *in vitro*, whereas engraftment of CD4+ T cells transduced with chimeric human/rhesus TRIM5CypA into a humanized mouse model also confers a resistance to HIV-1 infection [82,83,84**]. Phase I clinical trials of TRIM5CypA are planned for the near future [84**,85].

**CONCLUSION**

Although gene therapies hold out the prospect of a solution to many diseases that are not currently treatable, they do not represent a realistic opportunity to treat a large population of current HIV-infected people. Despite the optimistic outlook for future treatments, the reality is that last year nearly two million people became infected with HIV-1. This, combined with the fact that viral resistance to current therapies is beginning to be detected, dictates that innovative therapeutic options will be imperative for treatment of HIV infection in the near future.

**Acknowledgements**

*We would like to thank Dr Richard Sloan for critical discussion.*
Conflicts of interest

There are no conflicts of interest.

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