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HIV-1 and interferons: who's interfering with whom?

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Abstract

The ability of interferons (IFNs) to inhibit HIV-1 replication in cell culture models has long been recognized, and the therapeutic administration of IFNα to HIV-1-infected patients who are not receiving antiretroviral therapy produces a clear but transient decrease in plasma viral load. Conversely, studies of chronic HIV-1 infection in humans and SIV-infected animal models of AIDS show positive correlations between elevated plasma levels of IFNs, increased expression of IFN-stimulated genes (ISGs), biomarkers of inflammation and disease progression. In this Review, we discuss the evidence that IFNs can control HIV-1 replication *in vivo* and debate the controversial role of IFNs in promoting the pathological sequelae of chronic HIV-1 infection.

HIV-1 is a retrovirus of the genus *Lentivirus* that causes persistent infection of humans and arose from cross-species transmissions of SIV of chimpanzees in the first half of the twentieth century[1,2]. HIV-1 principally infects $CD4^+$ T cells and is the aetiological agent of AIDS, which is characterized by the loss of $CD4^+$ T cells, profound immunodeficiency and susceptibility to fatal opportunistic infections. Acute HIV-1 infection, which often manifests as a flu-like illness in infected patients, is marked by high levels of systemic viral replication and a partial depletion of $CD4^+$ T cells that disproportionally affects some compartments, such as the lymphoid tissue of the gut. After the first few weeks of infection, the development of immune responses against HIV-1, in particular the adaptive cytotoxic $CD8^+$ T cell response, leads to some control of viral replication, the establishment of a stable set-point plasma viral load and significant reconstitution of the $CD4^+$ T cell count. A clinically asymptomatic phase of infection follows, typically lasting 8–10 years and involving persistent HIV-1 replication, systemic immune activation and inflammation, and progressive $CD4^+$ T cell decline, ultimately leading to the development of AIDS.

Viral infections are sensed by components of the innate immune system called pattern recognition receptors (PRRs), which include mainly the membrane-based Toll-like receptors (TLRs) and the cytosolic retinoic acid inducible gene 1 (RIG-I)-like receptors (RLRs)[3]. PRRs recognize conserved chemical and structural features of pathogens called pathogen-associated molecular patterns (PAMPs), leading to the activation of signalling cascades that culminate in programmes of transcriptional induction and the release of, among other molecules, interferons (IFNs). IFNs, and particularly type I IFNs, are a family of pleiotropic

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pro-inflammatory and immunomodulatory cytokines that induce an antiviral state through the upregulation of hundreds of genes termed interferon-stimulated genes (ISGs) (FIG. 1).

The relationship between IFNs and HIV-1 infection has received escalating attention over the past decade owing to a number of important observations: IFNα (a family of type I IFNs) exerts a profound block on HIV-1 replication in cell culture models; the known anti-HIV-1 restriction factors, which are cellular proteins that inhibit viral replication, are themselves encoded by ISGs; acute HIV-1 infection of humans induces a wave of IFNα production in plasma; and IFNs seem to be capable of controlling HIV-1 replication in infected patients, as demonstrated by significant reductions in plasma HIV-1 viral load following therapeutic IFNα administration. Much of the associated research focus has been on identifying ISGs and their products that inhibit viral replication; as a result, a number of anti-HIV-1 ISGs have now been characterized (BOX 1).

In parallel, substantial effort has been made to understand the role, if any, of chronic IFN stimulation in the pathogenesis of AIDS. This body of work includes gene expression profiling studies of $CD4^+$ T cells from HIV-1-infected patients, as well as studies of pathogenic SIV infections of non-human primates (NHPs) (such as SIV infection of macaque monkeys), and has revealed that ISGs are among the genes that are abnormally upregulated during chronic pathogenic infections[4–6].

In this Review, we discuss recent advances in our understanding of the relationship between HIV-1 and the IFN system, and we try to reconcile the beneficial and detrimental roles of IFNs during natural HIV-1 infection.

IFN-mediated responses to HIV-1 infection

There are 3 families of IFNs, each of which signal through their respective receptors: type I IFNs, consisting in humans of IFNα (which has 13 subtypes), IFNβ, IFNuω, IFNε and IFNκ; type II IFN (that is, IFNγ); and type III IFNs, consisting of IFNλ1, IFNλ2, IFNλ3 and IFNλ4 (REFS 7,8. Antiviral responses primarily involve type I IFNs, which exhibit broad antiviral effects against multiple viruses in cultured cell models. Type I IFNs act in a paracrine and an autocrine manner to signal through the heterodimeric type I IFN receptor (IFNAR), which is composed of the subunits IFNAR1 and IFNAR2, leading to activation of the receptor-associated protein kinases tyrosine kinase 2 (TYK2) and Janus kinase 1 (JAK1) (FIG. 1). These kinases phosphorylate signal transducer and activator of transcription 1 (STAT1) and STAT2 to allow either homodimerization (for STAT1) or heterodimerization (STAT1–STAT2) and dimer translocation to the nucleus. STAT1–STAT2 dimers bind to IFN regulatory factor 9 (IRF9) to form the ISG factor 3 (ISGF3) complex, which binds to IFN-stimulated response elements (ISREs) in the promoters of ISGs, whereas STAT1 dimers engage gamma-activated sequences (GAS). Binding of STAT dimers to ISREs and GAS activates the transcription of hundreds of ISGs[9] (FIG. 1) (for a list of activated ISGs, see Interferome v2.01). Other STAT dimers, phosphoinositide 3-kinases (PI3Ks) and mitogen-activated protein kinases (MAPKs) can also be activated via signalling cascades downstream of IFNAR, leading to additional programmes of gene induction[10].

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In addition to genes that are clearly related to immunity and host defence, ISGs include genes involved in diverse cellular functions, such as transcription, translation, cytoskeletal organization, DNA damage repair, apoptosis and lipid metabolism[11]. Although there are many well-characterized ISGs (reviewed in REFS 12,13), the functions of the majority remain largely obscure. In the past few years, high-throughput platforms have been developed for characterizing the antiviral effects of ISG-encoded proteins both individually and in combination[14,15]. These platforms have identified ISGs displaying broad inhibition against a number of viral families as well as others with more specific antiviral activity[14,16]. Identification and functional characterization of these genes and their products should lead to a better understanding of both the mechanisms of innate antiviral resistance and the corresponding viral evasion mechanisms, and should provide a clearer picture of the mechanistic underpinnings for the therapeutic application of IFNs.

HIV-1 sensing by components of the IFN system

A number of PRRs are involved in HIV-1 sensing, including the cytoplasmic receptors cyclic GMP–AMP (cGAMP) synthase (cGAS) and IFNγ-inducible protein 16 (IFI16) — both of which recognize viral cDNA — and TLR7, which recognizes viral genomic RNA in endosomes (FIG. 2). Importantly, different cell types seem to have differing capacities to sense infection, with plasmacytoid dendritic cells (pDCs), a cell type that is rich in PRRs, clearly playing a central part in HIV-1 detection and IFNα production.

Several sensors for cytoplasmic DNA have been identified over the past few years (reviewed in REF. 17), and two such sensors, cGAS and IFI16, are capable of detecting HIV-1 cDNA following infection[18–22]. cGAS has been shown to be responsible for sensing of nascent HIV-1 cDNA in infected monocyte-derived dendritic cells (MDDCs)[18,20] as well as in the monocytic THP-1 cell line[18]. Following activation by DNA binding, cGAS catalyses the synthesis of a cGAMP isomer from ATP and GTP. This cyclic dinucleotide functions as a second messenger that binds to and activates stimulator of IFN genes (STING). STING then activates the inhibitor of NF-κB (IκB) kinase (IKK) and TANK-binding kinase 1 (TBK1), resulting in the induction of IFNs and other cytokines via the activation of the transcription factors nuclear factor-κB (NF-κB) and IRF3 (FIG. 2). Further support for the importance of the signalling pathways initiated by cGAS comes from the analysis of engineered HIV-1 viruses carrying mutations affecting the capsid (CA) region of the Gag protein[21]. Specifically, mutant viruses with substitutions at residues N74 or P90 induce the production of cGAMP and IFNs following infection of monocyte-derived macrophages (MDMs), whereas wild-type viruses do not[21]. These mutations prevent CA interactions with host cell proteins such as cyclophilin A (CYPA; also known as PPIA), nucleoporin 358 (NUP358; also known as RANBP2) and cleavage and polyadenylation specific factor 6 (CPSF6)[23], whereas it is thought that the recruitment of these host proteins to wild-type viral reverse-transcription complexes (RTCs) shields viral cDNA from sensing by cGAS (and possibly other PRRs)[21].

IFI16 is a pyrin and HIN domain-containing (PYHIN) protein and was identified as a protein bound to cytosolic DNA[24]. IFI16 induces IFN production via STING and IRF3 (FIG. 2). In cultured quiescent tonsillar $CD4^+$ T cells infected with HIV-1, in which cGAS is not

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expressed, IFI16 sensed incomplete HIV-1 DNA replication intermediates. In addition to stimulating IFN production, IFI16 activation induces caspase 1 activation and cell death by pyroptosis[19,25], in contrast to the caspase 3-mediated apoptosis observed in activated, productively infected T cells. Importantly, in *ex vivo* human lymphoid aggregate cultures infected with HIV-1, more than 95% of $CD4^+$ T cell death occurs in cells that are in a quiescent state[25,26], suggesting that IFI16-mediated pyroptosis may be a major contributing mechanism to the profound decline of $CD4^+$ T cells that characterizes chronic HIV-1 infection.

TLR7 has been shown to be essential for HIV-1 sensing by pDCs and mediates the recognition of viral genomic RNA in endosomes[27,28]. TLR7 activation causes recruitment of myeloid diffentiation primary response gene 88 (MYD88), which leads to the induction of IFNs and other cytokines through activation of IRF7 and NF-κB[29] (FIG. 2). *In vitro*, pDCs can efficiently sense HIV-1 free particles as well as virus-infected cells, leading to the production of high levels of IFNα[27,28]. The importance of pDC-mediated viral sensing is underscored by observations from humanized mice, in which depletion of pDCs almost completely abrogates the initial wave of IFN production seen during acute HIV-1 infection[30]. Additionally, in SIV-infected cynomolgus macaques, the natural reversal of IFN production is strongly associated with pDC exhaustion or death[31], and blockade of TLR7-mediated (and TLR9-mediated) virus sensing during acute SIV infection of macaques results in a diminution of IFN production[32], further highlighting the importance of TLR sensing *in vivo.* Interestingly, the production of IFNs in this context is not completely abrogated, consistent with the view that multiple sensors participate in viral detection[28,32].

In contrast to the production of IFNs by pDCs following infection, HIV-1 seems to avoid triggering an IFN response in many other cultured cells[21,33–35]. The host 3′-repair exonuclease 1 (TREX1) plays an important part in this respect by degrading excess HIV-1 cDNA[34], which may otherwise be sensed by cGAS or IFI16 (FIG. 2). For instance, in MDMs depleted of TREX1, HIV-1 cDNA induces IFN expression via STING, TBK1 and IRF3 (REF. 34). Therefore, there seems to be competition between recognition of HIV-1 cDNA by cytoplasmic receptors, masking of HIV-1 cDNA by cellular factors and clearance of HIV-1 cDNA by TREX1; the balance between these effects will have an impact on the IFN response and, presumably, pathogenic outcome in the infected host.

Finally, evidence has recently emerged that HIV-1 restriction and sensing can be mediated by the same proteins. For example, two HIV-1 restriction factors, the tripartite motif-containing protein 5α (TRIM5α) and tetherin (also known as BST2), can each detect particulate viral assemblies and initiate intracellular signalling via transforming growth factor-β-activated kinase 1 (TAK1, also known as MP3K7), TNF receptor-associated factor 6 (TRAF6) and NF-κB to enhance the expression of pro-inflammatory genes and cytokines[36–38].

The IFN-induced anti-HIV-1 effectors

Efforts to assign single ISG-encoded proteins as effectors of specific inhibitory mechanisms during the HIV-1 life cycle have been somewhat erratic until recently, although the focused

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screens that led to the identification of several HIV-1 and SIV restriction factors represent exceptions (BOX 1). Interestingly, these two topics are now merging, partly because restriction factors, although frequently expressed constitutively, are also induced to a degree by IFN[39,40] and partly because functional screening of cDNAs has become more experimentally mainstream.

HIV-1 restriction factors.

Restriction factors are dominantly acting, cell-intrinsic proteins that can potently suppress HIV and SIV replication. To date, four restriction factors have been unambiguously defined: TRIM5α; sterile α motif domain and histidine aspartic acid (HD) domain 1 (SAMHD1); apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3 (APOBEC3) proteins (specifically, APOBEC3G, APOBEC3D, APOBEC3F and certain allelic forms of APOBEC3H); and tetherin[41–46] (FIG. 3).These proteins share a number of features (BOX 2), and their mechanisms of action have been reviewed extensively[47,48]: TRIM5α, SAMHD1 and APOBEC3 proteins target the early post-entry phases of infection, and tetherin prevents viral release from infected cells (FIG. 3).

TRIM5α is an E3 ubiquitin ligase that binds to the CA lattice that forms the exterior surface of the post-entry viral cores. These viral cores normally mature into RTCs, but the TRIM5α–CA interaction leads to accelerated RTC fragmentation and prevents viral cDNA synthesis. SAMHD1 is a 2′-deoxynucleoside 5′-triphosphate (dNTP) triphosphohydrolase that depletes dNTP levels in non-dividing cells, thereby depriving reverse transcriptase of the substrates required for effective cDNA synthesis[49,50]. Interestingly, SAMHD1 has also been reported to be a nuclease that targets viral RNA for degradation[51]. APOBEC3 proteins are cytidine deaminases that are packaged into virions and remain associated with viral RTCs in newly challenged cells, where they suppress viral cDNA synthesis by interfering with the processivity of reverse transcription. In addition, they destructively hypermutate the cDNAs that are made by catalysing excessive C-to-U editing of (mostly) first-strand cDNA (also known as the minus strand). These mutations register as G-to-A transitions in the cDNA strand (also known as the plus strand) and compromise the genetic integrity of the virus. Finally, tetherin is a transmembrane protein that prevents the release of budded virions from the surface of infected cells by forming proteinaceous bridges between viral and cellular membranes (FIG. 3).

HIV-1 evasion of restriction factors.

One of the hallmarks of restriction factors (BOX 2) is that HIVs and SIVs have evolved an array of evasion mechanisms such that these proteins are commonly regarded as ineffective at controlling viral replication in cells of the natural host. For example, human restriction factors have little, or only minor, impact on HIV-1 transmission and replication in the context of human infections. By contrast, restriction factors tend to be very effective at blocking HIV or SIV infection of unnatural hosts, owing to the inability of viral evasion mechanisms to function efficiently in non-cognate species[52]. As a consequence, restriction factors are viewed as influential barriers to cross-species transmission[53].

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The viral accessory proteins viral infectivity factor (Vif) and viral protein unique (Vpu) serve as countermeasures for the APOBEC3 proteins and tetherin, respectively. Vif interacts with APOBEC3 proteins and induces the recruitment of an E3 ubiquitin ligase complex containing the scaffold protein cullin 5 (CUL5) and the substrate adaptors elongin B (ELOB; also known as TCEB2) and ELOC (also known as TCEB1), which leads to polyubiquitylation and proteasomal degradation of APOBEC3 proteins[54,55]. Similarly, Vpu interacts with tetherin, preventing tetherin trafficking to the cell surface and promoting tetherin ubiquitylation and subsequent degradation in endolysosomes[56]. Human TRIM5α does not suppress HIV-1 because it fails to engage and disrupt the post-entry CA lattice effectively. Escape from SAMHD1 is less well understood and may in fact be a 'red herring', as the importance of HIV-1 infection of myeloid cells *in vivo* remains questionable. Interestingly, the related virus HIV-2 encodes an accessory protein, viral protein X (Vpx), which induces SAMHD1 ubiquitylation and degradation through the recruitment of an E3 ubiquitin ligase complex that contains CUL4A, DNA damage-binding protein 1 (DDB1) and DDB1–CUL4-associated factor 1 (DCAF1; also known as VPRBP). This activity of Vpx suggests that HIV-2 needs to avert SAMHD1 function for replication *in vivo*. Therefore, the absence of a similar activity in HIV-1 may point to the possible irrelevance of SAMHD1 during natural infection or may indicate that SAMHD1 serves to assist HIV-1 in avoiding sensing in myeloid cells. Furthermore, the reverse transcriptase of HIV-1 can still catalyse DNA synthesis in the presence of low dNTP concentrations, including those found in non-proliferating myeloid cells, indicating that SAMHD1 activity in these cells does not prevent HIV-1 replication[57].

Although human restriction factors do not induce pronounced anti-HIV-1 phenotypes in the context of infection with wild-type viruses, there is good evidence that subtle contributions take place during natural infection. In reality, the actions of a restriction factor and its counterbalancing evasion mechanism are likely to be in a state of equilibrium such that neither exhibits complete dominance. Examining the interaction between Vif and APOBEC3 illustrates this equilibrium, as incomplete Vif function (for example, due to allelic variation) or increased APOBEC3 activity (as occurs following IFN induction or treatment[58], or on account of intrinsic expression differences) could shift this balance and promote APOBEC3-mediated effects. Indeed, this must happen during natural HIV-1 infection, as G-to-A hypermutated viral sequences are readily detected[59], viral sequence evolution takes place at sites of APOBEC3 editing[60,61], and higher APOBEC3 expression levels correlate with clinical benefit[62]. Whether variation in the balance between other restriction factors and their corresponding escape pathways, including the modulatory effects of IFNs[63], can affect *in vivo* HIV-1 infection and disease progression remains to be determined.

HIV-1 resistance factors.

Given evidence from cell culture models that treatment with IFNs can potently suppress HIV and SIV replication[64–69], there is an enduring interest in discovering additional anti-HIV and anti-SIV ISGs. Indeed, the observation that IFNα treatment imparts a strong post-entry block to retrovirus infection at the level of viral cDNA accumulation and integration[68,69] provoked cDNA screens that led to the identification of myxovirus resistance 2 (MX2) as a significant inhibitor of HIV-1 infection in IFN-treated cultured cells[70–72].

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MX2 is an IFN-inducible dynamin-like GTPase, although this enzymatic function appears to be dispensable for viral inhibition[70,72]. Human MX2 localizes to the nuclear envelope, nuclear pore complexes and cytoplasmic puncta[72–74], and inhibits divergent HIV-1 strains, but it is less effective against SIVs and inactive against other retroviruses, such as murine leukaemia virus (MLV)[70]. Viral inhibition occurs after substantial cDNA synthesis, in contrast to the earlier blocks described for the APOBEC3 proteins, TRIM5α and SAMHD1. Although the mechanism of viral inhibition mediated by MX2 is unknown, it may involve direct interactions with the viral CA protein[70–72,75,76] and is manifested as a failure of viral cDNA to enter and accumulate in the nucleus[70,72] (FIG. 3).

There is growing evidence for the existence of additional IFN-activated mechanisms of HIV-1 control. For example, the IFN-induced transmembrane (IFITM) proteins — specifically, IFITM1, IFITM2 and IFITM3 — are found in various cellular membranes and are incorporated into the viral membrane[77,78]. In contrast to the quantitative effect of tetherin on viral release, the IFITM proteins interfere with membrane fusion through the combined effects of increasing curvature, decreasing fluidity and altering membrane composition; as a result, IFITM proteins can act in virus particles or in target cells to impede viral entry[77–79] (FIG. 3).

A further example is schlafen 11 (SLFN11), which inhibits virion production by suppressing HIV-1 protein synthesis[80] (FIG. 3). SFFN11 is a cytoplasmic RNA-binding protein that selectively represses the translation of mRNAs with a codon bias different from that of typical human mRNAs — such as those expressed by HIV-1. This inhibitory mechanism may involve the binding of SLFN11 to tRNAs and their subsequent inactivation or removal.

Much remains to be learnt regarding the molecular details of MX2-, SFLN11- and IFITM-mediated inhibition of HIV-1, and searching for further ISG-encoded proteins that suppress early reverse transcription or other stages of viral replication remain active areas of current investigation. Interestingly, HIV-1-mediated mechanisms for evading MX2-, SLFN11- or IFITM-mediated suppression of viral replication have not been reported, making these ISG-encoded proteins fundamentally different to the restriction factors discussed above, which are either neutralized or avoided by HIV-1 evasion strategies. Accordingly, MX2, IFITM proteins and SLFN11 are more appropriately classified as resistance factors and are good candidates for host proteins that contribute to HIV-1 control during acute infection.

The beneficial roles of IFNs

Studies in different animal models have demonstrated the importance of the IFN system in controlling HIV and SIV infections.

IFNs in the control of acute infection.

IFNAR-deficient mice are highly susceptible to infection with a range of different viruses (reviewed in REF. 81). IFNs are also crucial for the control of lentiviral infections of NHPs[82]. For example, in a pathogenic SIV rhesus macaque model using intrarectal challenge, administration of an IFNAR antagonist led to higher viral loads during acute infection than in untreated controls, and treated animals progressed to AIDS and death

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within 30 weeks post-infection, whereas all untreated control animals survived through the 44-week follow-up[82]. Using the same model, pegylated-IFNα2a administration before and during viral challenge and for the subsequent 4 weeks after infection reduced the frequency of viral transmission[82]. Therefore, an intact IFN response during acute lentiviral infection seems to be crucial for viral control and the amelioration of subsequent disease and, when stimulated, can help to suppress initial viral transmission.

Importantly, this state of relative SIV suppression in IFN-treated macaques was not durable, as ISGs were downregulated within the first few weeks of IFNα treatment, and viral loads became higher than in untreated controls once the animals were infected. Downregulation of ISGs was associated with upregulation of the gene encoding forkhead box O3a (FOXO3a), which is a negative regulator of IFN signalling, suggesting that desensitization to the IFN response was a result of endogenous homeostatic control. Furthermore, corroborating the findings of these NHP studies, which indicate a beneficial role of IFNs during the early stages of infection, depletion of pDCs in a humanized mouse model of HIV-1 infection leads to reduced production of IFNα and to increased HIV-1 replication in the acute phase[30]. However, in contrast to the marked T cell decline observed in primates, the subsequent loss of T cells in these humanized mice was much less severe[30].

As noted above, primary HIV-1 infection of humans is followed by an intense cytokine storm involving IFNα (from a median baseline of 4.6 pg ml^{-1} to a median peak of 37.5 pg ml^{-1}) and many other pro-inflammatory and immunomodulatory cytokines[83] that collectively precede the establishment of the set-point viral load. In addition, transmitted/founder viruses (T/F viruses) are commonly less sensitive to inhibition by IFNα in cultured cell models than the corresponding viruses that are present during chronic infection, suggesting that resisting the inhibitory effects of IFNα may provide a selective advantage during transmission and acute infection[84,85]. Taken together, these observations demonstrate that a robust type I IFN response helps to control initial HIV and SIV infection.

Clinical effects of IFN treatment on HIV-1 infection.

The virological benefits of administering IFNα to patients infected with HIV-1 have been recognized for some years. In the pre-highly active antiretroviral therapy (HAART) era, a randomized controlled trial of 12 weeks of IFNα2b treatment was conducted in asymptomatic patients infected with HIV-1; this trial showed that treatment led to a decrease in the frequency of viral isolation by culture and fewer patients developing AIDS during follow-up relative to patients receiving placebo[86]. However, interest in the use of IFNs for the control of HIV-1 infection declined with the development and introduction of HAART in the later 1990s. Nonetheless, the capacity of IFNα to reduce the plasma HIV-1 viral load was recognized and characterized in the context of its administration for other conditions such as hepatitis C virus (HCV) co-infection and Kaposi sarcoma[87,88].

A more recent study investigated the virological and immunological effects of 12 weeks of pegylated-IFNα treatment in patients who were infected with HIV-1 alone and who were immunologically stable in the absence of HAART[89]. Weekly virological analysis showed that IFNα treatment induced a rapid decline in viral load, which reached a nadir at 2 weeks with a median reduction of 1.3 log_{10} copies ml^{-1} from baseline. This rapid initial decline in

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viral load following treatment with IFNα was followed by a partial rebound in HIV-1 viraemia prior to treatment discontinuation (FIG. 4). Follow-up work has examined the expression levels of a set of canonical ISGs, including MX2, in the peripheral blood mononuclear cells (PBMCs) of these patients and found correlations between sustained ISG upregulation and viral-load reduction[90].

Interestingly, a minority of patients did not exhibit a significant reduction in viral load, and this lack of response was associated with high baseline expression of ISGs in PBMCs and poor upregulation of ISGs following treatment. Interestingly, similarly poor ISG responses have been noted in hepatocytes of patients who are infected with HCV and fail to respond to IFN-based therapy[91]. Notably, although IFNα treatment induces sustained ISG induction in human PBMCs, this is not always observed in NHPs. For example, a reversal of ISG induction was seen in rhesus macaques after the first week of treatment (with or without acute SIV infection)[82] and between weeks 3 and 12 in studies of SIV-infected sooty mangabeys[92]. The basis for this difference between humans and NHPs is not understood, but probably reflects important points of variation in the biology of NHP models of SIV infection and human HIV-1 infections.

The maintenance of ISG expression throughout the 12 weeks of IFNα therapy in humans raises the question of what events underpin the partial reversal of the viral-load decline seen early in therapy. One possibility is that HIV-1 evolves to escape the activity of IFN-induced effectors. Indeed, there is some evidence that Vpu evolution during IFNα treatment leads to the selection of alleles that downregulate tetherin more effectively[58]. Similarly, the IFN-induced upregulation of APOBEC3 proteins may contribute to increased rates of HIV-1 evolution[61]. Nevertheless, despite the limitations of IFNα monotherapy described above, another study has shown that treatment with IFNα alone appears to be capable of maintaining virological suppression (defined as fewer than 400 HIV-1 copies ml^{-1}) for at least 12 weeks after HAART discontinuation in 45% of patients with prior virological control on HAART[93]. Although this subject is not the focus of this Review, it is possible that IFNα also enhances the antiviral activity of many different immune cells, and this would potentially contribute to improved viral control (BOX 3).

There has been some interest in the potential use of IFNs in HIV-1 eradication efforts. It has been reported that for patients who are co-infected with HIV and HCV and who are receiving IFNα-based therapy combined with HAART, there is a reduction in total and integrated (proviral) HIV-1 DNA levels in PBMCs[94]. Similar results were seen in patients who maintained virological suppression when treated with IFNα monotherapy after HAART discontinuation (see above)[93]. Although the overall effects were modest and effects between patients were highly variable, it is important to ascertain the underlying mechanism, particularly in the context of patient stratification based on general IFN responsiveness (that is, the extent of ISG upregulation from baseline levels). This report and others may hint at a potential role for IFNα in decreasing the size of the HIV-1-infected cellular reservoir, a highly desirable step with direct relevance for HIV-1 cure efforts[95].

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The detrimental roles of IFNs

In contrast to the studies reporting the beneficial roles of IFNs during acute SIV infection and the virological effects of IFN treatment during HIV-1 infection, several studies associate IFN signalling and stimulation of ISGs with progressive HIV or SIV-related disease. In the chronic phase of HIV-1 infection, a positive correlation between the plasma levels of IFNα and the plasma HIV-1 viral load has been reported, and there is an inverse correlation between the plasma levels of IFNα and $CD4^+$ T cell counts[96].

Numerous studies have characterized the gene expression profiles of $CD4^+$ T cells isolated from patients who are infected with HIV-1 and who exhibit different viral loads and different rates of disease progression[4–6]. In general, patients with higher viral loads, increased rates of disease progression and later-stage HIV-1 infection have increasingly abnormal $CD4^+$ T cell gene expression profiles. In addition to a pronounced increase in the expression of genes involved in the cell cycle, these studies show a relative overexpression of ISGs in patients with higher viral loads and faster rates of disease progression. These observations led to the hypothesis that chronic IFN signalling and generalized inflammation may be partially responsible for $CD4^+$ T cell dysfunction and loss during chronic HIV-1 infection. According to this model, IFN signalling and other drivers of $CD4^+$ T cell activation, such as viral antigens and microbial translocation, increase the available number of activated $CD4^+$ T cells, which are the permissive substrates for productive viral infection, and thereby facilitate HIV-1 replication. This promotes the establishment of a detrimental and perpetual cycle of immune activation and viral replication, as well as cell death through various mechanisms, among which may be IFN-dependent apoptosis mediated by tumournecrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)[97]. Furthermore, IFNα can have inhibitory effects on cell-mediated immunity through the production of immunosuppressive cytokines such as interleukin-10 (IL-10) and the upregulation of ligands for inhibitory receptors such as programmed death ligand 1 (PDL1), and these effects may contribute further to the loss of HIV-1 immune control[10,98–100]. A cautionary interpretation of such studies that relate disease markers to both plasma IFNα levels and ISG expression is that activation of the IFN system in individuals with more advanced disease might simply be a consequence of increased viral replication, and that similar correlations could be made for many other pro-inflammatory or antiviral cytokines.

Observations from different NHP SIV models have been influential in suggesting a role for IFNα in the pathogenesis of HIV and SIV infection, particularly through the comparison of pathogenic models — those in which the SIV-infected animals generally succumb to the development of AIDS, such as SIVmac infection of macaques — with non-pathogenic models — those in which an SIV infection of a particular NHP host does not appear to cause disease, such as SIVagm infection of African green monkeys. As with HIV-1 infection of humans, IFNα levels correlate positively with viral load and negatively with $CD4^+$ T cell count in pathogenic NHP models[101]. Furthermore, immune responses during the acute phase of SIV infection have been extensively investigated in pathogenic and non-pathogenic NHP models in order to identify immune signatures that could provide an explanation for the differences in subsequent disease outcomes[102–104]. Gene expression profiling of $CD4^+$ T cells from blood and lymph nodes have reproducibly demonstrated the upregulation of ISGs

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in the acute phase of SIV infection in both pathogenic and non-pathogenic models. However, in the non-pathogenic models, the upregulation of ISGs and the expression of immune activation markers are reversed during the first few weeks post-infection, and subsequent viral replication occurs in the absence of further IFN stimulation or immune hyperactivation[102–104]. By contrast, in the pathogenic models, the upregulation of ISGs is maintained over time. Although the basis for this dichotomy remains poorly understood, these data suggest that sustained IFN-mediated stimulation could contribute to disease pathogenesis. Interestingly, administration of high-dose IFNα to African green monkeys (a non-pathogenic model) from days 9 to 24 post-infection does not impede the resolution of immune activation and the reversal of ISG induction seen during the primary infection[105], suggesting that other inflammatory mediators may be responsible for the continuing ISG elevation and immune activation that are a hallmark of pathogenic infections.

In summary, there are reproducible associations between levels of IFNα in plasma, expression of ISGs in $CD4^+$ T cells and disease progression in HIV-1 or SIV infection. In addition, the downregulation of ISG expression after the acute SIV infection appears to distinguish non-pathogenic from pathogenic infections of NHPs. Taken together, these findings point towards dysregulation of IFN signalling pathways in chronic persistent HIV or SIV-related disease, although a more causal role for type I IFNs in pathogenesis remains to be proved.

Conclusion and outlook

IFNα is capable of suppressing HIV-1 replication in infected patients, and an intact IFN response seems to be crucial for the control of acute lentiviral infection of primates and for control of subsequent disease. IFNs are thought to control HIV-1 replication principally through the upregulation of ISGs in the target cells for infection. In addition to the IFN-mediated increase in the expression of HIV-1 restriction factors, which may assist in overcoming viral evasion and escape mechanisms, the recently identified HIV-1 resistance factors MX2, SLFN11 and IFITMs may also be important for this response. However, several aspects of the role of IFNs during HIV-1 infection require further investigation, and future studies should aim to: identify pathways of HIV-1 detection in all infected cell types, including activated $CD4^+$ T cells; determine the relevance of HIV-1 sensing in non-productively infected cells for pathogenesis; and define additional HIV-1-suppressive ISGs, such as those responsible for the early post-entry block to HIV-1 infection.

A more complete understanding of the *in vivo* mechanism (or mechanisms) of HIV-1 viral-load reduction during IFNα treatment is a central research focus, and there are several key questions relating to this that should be addressed. Which ISGs are important *in vivo*? Do other IFN-stimulated branches of the immune system, such as natural killer cells, B cells and T cells, contribute to these mechanisms? Does HIV-1 escape from these effector mechanisms, or is the host response limited by reversal of the type I IFN responses at the immunological level? Are type I IFNs capable of reducing HIV-1 DNA loads in $CD4^+$ T cells, and if so, what is the underpinning biology? In addition, findings in NHP models indicate that pre-exposure prophylactic strategies that rely on the use of IFNs might be

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beneficial for controlling many viral infections, but future studies are needed to determine the optimal timing for such interventions.

In summary, there is a complex relationship between HIV-1 sensing by the innate immune system, the evocation of antiviral states, the pathways of viral evasion, and the induction and perpetuation of pathogenic cellular processes. Deciphering this relationship will require incisive molecular and translational research. We envisage that further elucidating the interplay between HIV-1 and the IFN system will yield broadly applicable principles for understanding many viral infections and will help to guide future intervention and therapeutic strategies.

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Glossary

Retrovirus

A positive-sense single-stranded RNA virus of tire family *Retroviridae*. These viruses replicate via a DNA intermediate that is synthesized by the reverse transcriptase enzyme. Retroviruses integrate their DNA into the host cell chromosome.

Lentivirus

A particular genus of retroviruses that are primarily characterized by infections with long clinical incubation periods, often years to decades. Lentiviruses infect primate and non-primate hosts.

Set-point plasma viral load

The semi-stable plasma level of HIV-1 RNA that is readied after the period of acute HIV-1 infection in most patients, in the absence of antiretroviral therapy

Pattern recognition receptors

(PRRs). Germ line-encoded receptors that recognize the pathogen-associated molecular patterns which characterize pathogenic microorganisms.

Pathogen-associated molecular patterns

(PAMPs). Biomolecules of diverse nature (ranging from lipopolysaccharides to forms of nucleic acids) that are characteristic of pathogenic microorganisms.

Apoptosis

A mode of programmed cell death that leads to the elimination of the cell without the release of inflammatory mediators.

Plasmacytoid dendritic cells

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(pDCs). DCs that are specialized in the detection of microbial pathogens and the production of interferon-α (IFNα). pDCs are thought to be particularly important for HIV-1 sensing.

Monocyte-derived dendritic cells

(MDDCs). DCs that have been derived by inducing their differentiation from primary monocytes *in vitro*.

Monocyte-derived macrophages

(MDMs). Macrophages that have been derived by inducing their differentiation from primary monocytes *in vitro*.

Reverse-transcription complexes

(RTCs). Complexes of viral nucleic acid, viral proteins (for example, reverse transcriptase) and cellular proteins that mediate viral DNA synthesis. RTCs are derived from viral capsids following virus entry into the cytoplasm during infection.

Pyroptosis

A mode of programmed cell death that leads to the release of mediators of inflammation and that is often triggered by recognition of pathogenic microorganisms.

Lymphoid aggregate cultures

Cultures composed of small blocks of lymphoid tissue usually derived from the tonsils or the spleen. This experimental system is used in an attempt to replicate the spatial organization and cytokine milieu of *in vivo* lymphoid tissue.

Humanized mice

Mice that congenitally lack T cells, B cells and natural killer cells, and that are transplanted with human haematopoietic stem cells, leading to the reconstitution of a human-derived immune system.

Nuclear pore complexes

Large protein complexes that form the channels in the nuclear envelope which allow the transport of molecules between the nucleus and the cytoplasm.

Pegylated

Covalently conjugated to polyethylene glycol (PEG). This alters the pharmacokinetic behaviour of a drug, allowing the dosing frequency to be reduced in the case of interferon-α (IFNα).

Transmitted/founder viruses

(T/F viruses). Viruses that are responsible for the establishment of initial HIV-1 infection and from which the viral population seen in later infection is thought to be derived.

Highly active antiretroviral therapy

(HAART). A combination of antiretroviral drugs used to suppress HIV replication.

Kaposi sarcoma

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A common tumour associated with advanced HIV-1 infection. The tumour is caused by human herpesvirus 8 (HHV8) and presents as a purplish-brown vascular lesion either on the skin or in internal organs.

HIV-1 eradication

Clearance of replication-competent HIV-1 from the body of an infected person. Achieving this goal is generally thought to require the inhibition of any ongoing HIV-1 replication during conventional antiretroviral therapy and the elimination of infected cells harbouring latent (or transcriptionally inactive) but replication-competent HIV-1. The term reservoir is generally used to denote the pool of latently infected cells.

Microbial translocation

The emergence of microorganisms and microbial products, into the portal and systemic circulation from the gut, owing to compromise of the host gastrointestinal immune system.

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Box 1 |

The discovery of HIV and SIV restriction and resistance factors

APOBEC3G

Viral infectivity factor (Vif) is required for HIV-1 replication in primary cells and some cell lines. APOBEC3G (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G) was discovered through correlative RNA expression profiling and functional screening for cDNAs that, when expressed in virus-producing cells, inhibit infection by *vif*-deficient HIV-1. Subsequent work by many groups revealed that the related proteins APOBEC3D and APOBEC3F, as well as some variants of APOBEC3H, also suppress HIV-1 infection[41].

TRIM5α

Analyses of divergent retroviruses in cells from various species, as well as the identification of Fv1 as a post-entry suppressor of infection with Murine leukaemia virus[106], pointed to the existence of species-specific inhibitors of HIV-1. Functional screening of rhesus macaque cDNAs for suppressors of HIV-1 infection in target cells revealed rhesus tripartite motif-containing protein 5α (TRIM5α) as an early post-entry inhibitor of HIV-1 (REF. 42).

Tetherin

HIV-1 viral protein unique (Vpu) is essential for efficient virion release from some cell types, a phenotype that is exacerbated by interferon-α (IFNα) treatment in some cell types. Tetherin was identified through correlative RNA expression profiling and functional screening of cDNAs that inhibited the release of *vpu*-deficient HIV-1 particles from cells[45,46].

SAMHD1

The HIV-2 viral protein X (Vpx) promotes infection of myeloid cells, most notably plasmacytoid dendritic cells (pDCs). The finding that Vpx engages an E3 ubiquitin ligase containing cullin 4A (CUL4A), DNA damage-binding protein 1 (DDB1) and DDBl-CUL4-associated factor 1 (DCAF1) suggested that Vpx interacts with a cellular inhibitor of infection to promote the ubiquitylation and proteasomal degradation of this inhibitor. Affinity chromatography using Vpx as the ‘bait’ identified SAMHD1 (SAM and HD domain-containing protein 1) as this interacting factor, and the post-entry suppressor activity of SAMHD1 was revealed in postmitotic target cells[43,44].

IFITM

IFNα inhibits the production of infectious HIV-1 from certain cell lines. RNA silencing-based screening of IFN-stimulated genes (ISGs) was carried out on HIV-1-infected cells treated with IFNα, and this approach identified IFN-induced transmembrane protein 1 (IFITM1) as a suppressor of virus infectivity. Follow-up experiments showed that IFITM2 and IFITM3 can also inhibit HIV-1 (REF. 77).

SLFN11

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Schlafen (SLFN) proteins are encoded by ISGs, and the differential expression of SLFN11 between 293 cells and 293T cells guided its assignment as a negative regulator of HIV-1 mRNA translation[80].

MX2

The inhibitory effects of IFNα on the early stages of HIV-1 infection vary between cell lines and types. Transcriptomics-based screens guided the functional testing of ISG cDNAs for post-entry inhibitors of wild-type HIV-1 infection. The link between myxovirus resistance 2 (MX2) and IFN-mediated suppression was confirmed using *MX2*-directed RNA silencing approaches[70–72].

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Box 2 |

Hallmarks of HIV and SIV restriction factors

Restriction factors that target HIV and SIV are dominantly acting, cell-intrinsic proteins that can potently suppress HIV and SIV replication and that share a number of features.

Germ line encoded

Restriction factors are antiretroviral proteins that are invariant within an individual and are not altered through gene rearrangement or somatic mutation.

Inducible by IFNs

Restriction factors are typically expressed constitutively in many cell types but can also be induced by interferons (IFNs) in some cells, such as macrophages.

Cell autonomous

Restriction factors are sufficient to mediate viral suppression when expressed in single virus-producing cells or viral target cells. Communication with other cells is not required for activity.

Inactive against wild-type viruses replicating in their natural hosts

Owing to effective virally encoded evasion or escape mechanisms, restriction factors are essentially inactive against wild-type viruses in their natural hosts. For example, HIV-1 viral infectivity factor (Vif) preserves viral replication in human cells because it is an efficient antagonist of human APOBEC3 (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3) proteins. Similarly, HIV-1 capsid structures are not recognized by human tripartite motif-containing protein 5α (TRIM5α).

Barriers against cross-species transmission

Despite being essentially inactive against viruses replicating in their natural hosts, restriction factors are potent antiviral effectors against viruses from other host species. For example, HIV-1 Vif fails to antagonize APOBEC3 proteins from African green monkeys, resulting in effective suppression of wild-type HIV-1 in African green monkey cells. Similarly, HIV-1 capsids are efficiently recognized and inhibited by TRIM5α of rhesus macaques. Therefore, restriction factors are thought to be important barriers against cross-species transmission of primate immunodeficiency viruses.

Frequently downregulated or suppressed by viral accessory proteins

Vif antagonizes APOBEC3 proteins, viral protein unique (Vpu) antagonizes tetherin, and HIV-2 viral protein X (Vpx) antagonizes SAM and HD domain-containing protein 1 (SAMHD1). The exception is TRIM5α, the functionality of which is determined not by the interference of an accessory protein but rather by an interaction with the capsid (CA) lattice of post-entry viral cores.

Under Darwinian selection

The coding sequences of restriction factors display the hallmarks of Darwinian selection, as sequence variation in some positions has a propensity to be characterized by a high

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dN/dS ratio — which is the number of nonsynonymous substitutions per nonsynonymous site (dN) divided by the number of synonymous substitutions per synonymous site (dS). This feature can be indicative of host–pathogen co-evolution, and the sites under this selection may represent sequences encoding protein regions involved in direct pathogen contact, such as the binding site for Vif in APOBEC3G.

Regulated by protein degradation

The function or downregulation of restriction factors typically involves the cellular ubiquitin–proteasome system, which is involved in protein degradation. For example, Vif binds to and recruits APOBEC3 proteins to an E3 ubiquitin ligase complex containing cullin 5 (CUL5), elongin B (ELOB) and ELOC, and this leads to polyubiquitylation and proteasomal degradation of APOBEC3 proteins; furthermore, TRIM5α is itself a ubiquitin ligase.

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Box 3 |

Regulation of immune cells by type I IFNs

Although there is convincing evidence that upregulation of interferon (IFN)-stimulated gene (ISG) expression contributes to cell-autonomous resistance to infection and is an important component of the prophylactic and therapeutic effects of IFNα, there is debate about the role of other immune effector mechanisms in mediating the beneficial effects observed during these responses. For example, both direct and indirect effects of type I IFNs have been described for almost all immune cells and, for many cells types, type I IFNs can stimulate or inhibit effector functions depending on the timing and context of the exposure (reviewed in REF. 98).

Natural killer (NK) cells and $CD8^+$ T cells have a recognized role in the clearance of virally infected cells. Type I IFNs are important regulators of NK cell function and promote their activation and proliferation through the induction of interleukin-15 (IL-15)[107–109]. IL-15 production occurs directly in NK cells, through signalling via type I IFN receptor (IFNAR) and also from IFN-activated conventional dendritic cells (DCs)[109]. Type I IFNs are also important for the survival of antiviral $CD8^+$ effector T cells, and removal of IFN signalling during $CD8^+$ T cell activation limits their proliferation[100,110]. Type I IFNs induce the apoptosis of memory $CD4^+$ and $CD8^+$ T cells[111] and of regulatory T cells during acute viral infection[112], and this may facilitate the development of an optimal functional cytolytic T cell response[100].

Studies in non-human primate (NHP) models of SIV infection point towards the importance of NK cells, as opposed to T cells, in mediating protective type I IFN responses. IFNα2a treatment of macaques leads to resistance to SIV infection via rectal challenge, and this resistance is associated with ISG upregulation in various cell types, and also with increased frequencies of $CD56^+$ NK cells in the blood and of $CD16^+$ NK cells in the rectum[82]. SIV-specific $CD4^+$ and $CD8^+$ T cell responses are not affected by IFNα2a treatment in this model, suggesting that these cell types do not play a crucial part in the observed IFNα-induced protection. Similarly, treatment with a type I IFN antagonist before SIV infection suppressed ISG induction and NK cell numbers at >12 weeks post-infection, but had no observable effect on $CD4^+$ or $CD8^+$ T cell responses[82]. Supporting these findings, treatment of chronically SIV-infected sooty mangabeys with a recombinant type I IFN agonist decreased the SIV viral load — similar to the effect observed for IFNα treatment in humans infected with HIV-1 — but had no effect on SIV-specific $CD8^+$ T cells responses[92].

Type I IFNs have also been shown to enhance B cell-mediated immune responses[113] and probably facilitate other adaptive immune responses indirectly. For example, type I IFN-mediated activation and maturation of DCs and other antigen-presenting cells leads to increased antigen presentation, the secretion of cytokines and chemokines, and the presence of co-stimulatory signals[114].

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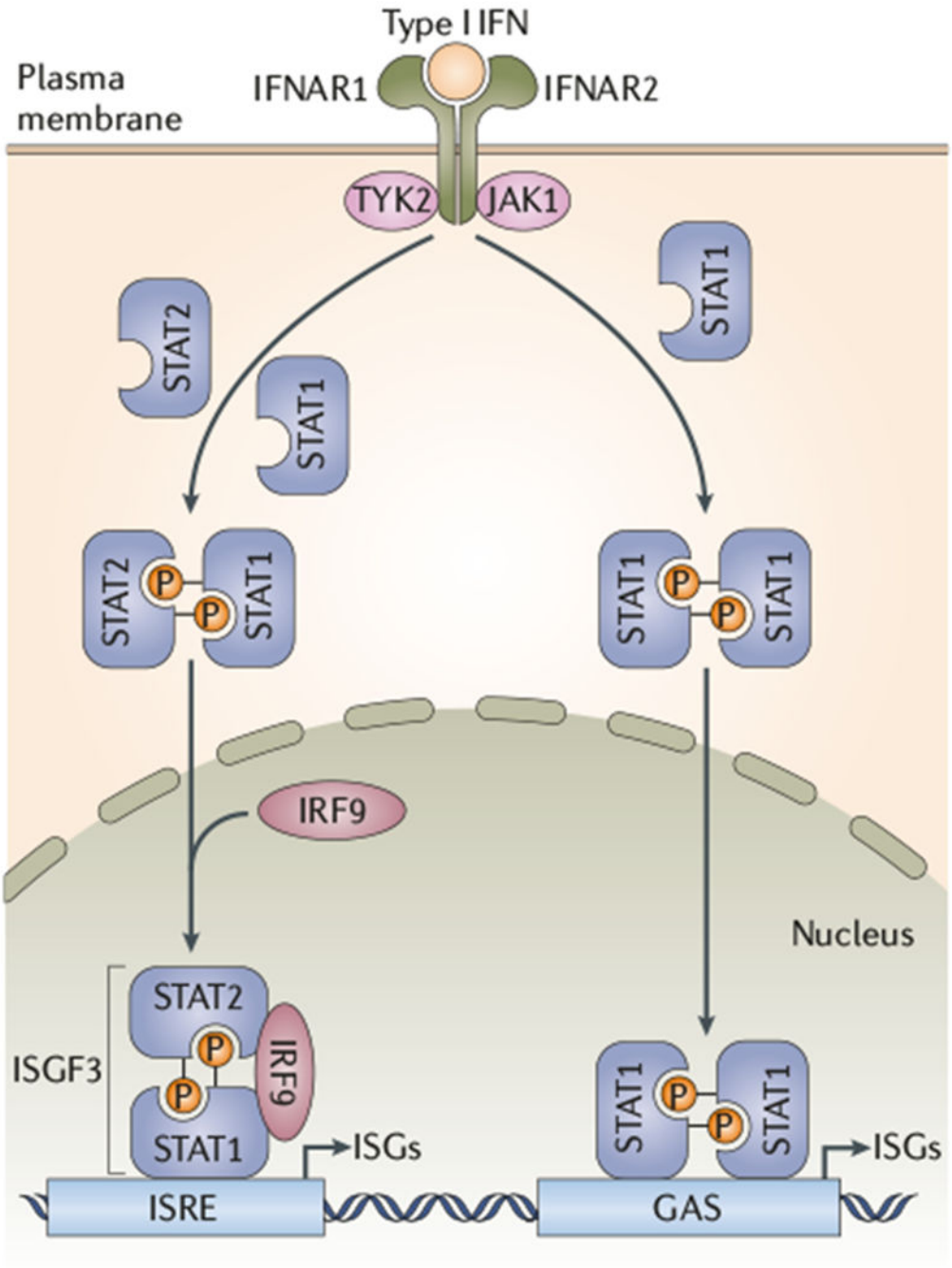

Figure 1 |. Induction of ISG expression.

Type I interferons (IFNs) bind to type I IFN receptor (IFNAR), which is composed of IFNAR1 and IFNAR2 subunits, leading to tyrosine kinase 2 (TYK2) and Janus kinase 1 (JAK1) activation. These kinases phosphorylate (P) signal transducer and activator of transcription 1 (STAT1) and STAT2 to allow homodimerization (for STAT1) and heterodimerization (STAT1 plus STAT2). These STAT dimers then translocate to the nucleus. STAT1–STAT2 dimers to bind interferon regulatory factor 9 (IRF9) to form the interferon-stimulated gene factor 3 (ISCF3) complex, which engages IFN-stimulated

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response elements (ISREs), whereas STAT1 homodimers engage gamma-activated seguences (GASs). Binding of the STAT dimers to ISREs and GASs activates transcription of IFN-stimulated genes (ISGs). Other STAT dimers, phosphoinositide 3-kinases and mitogen-activated protein kinases may also be activated downstream of type I IFNs.

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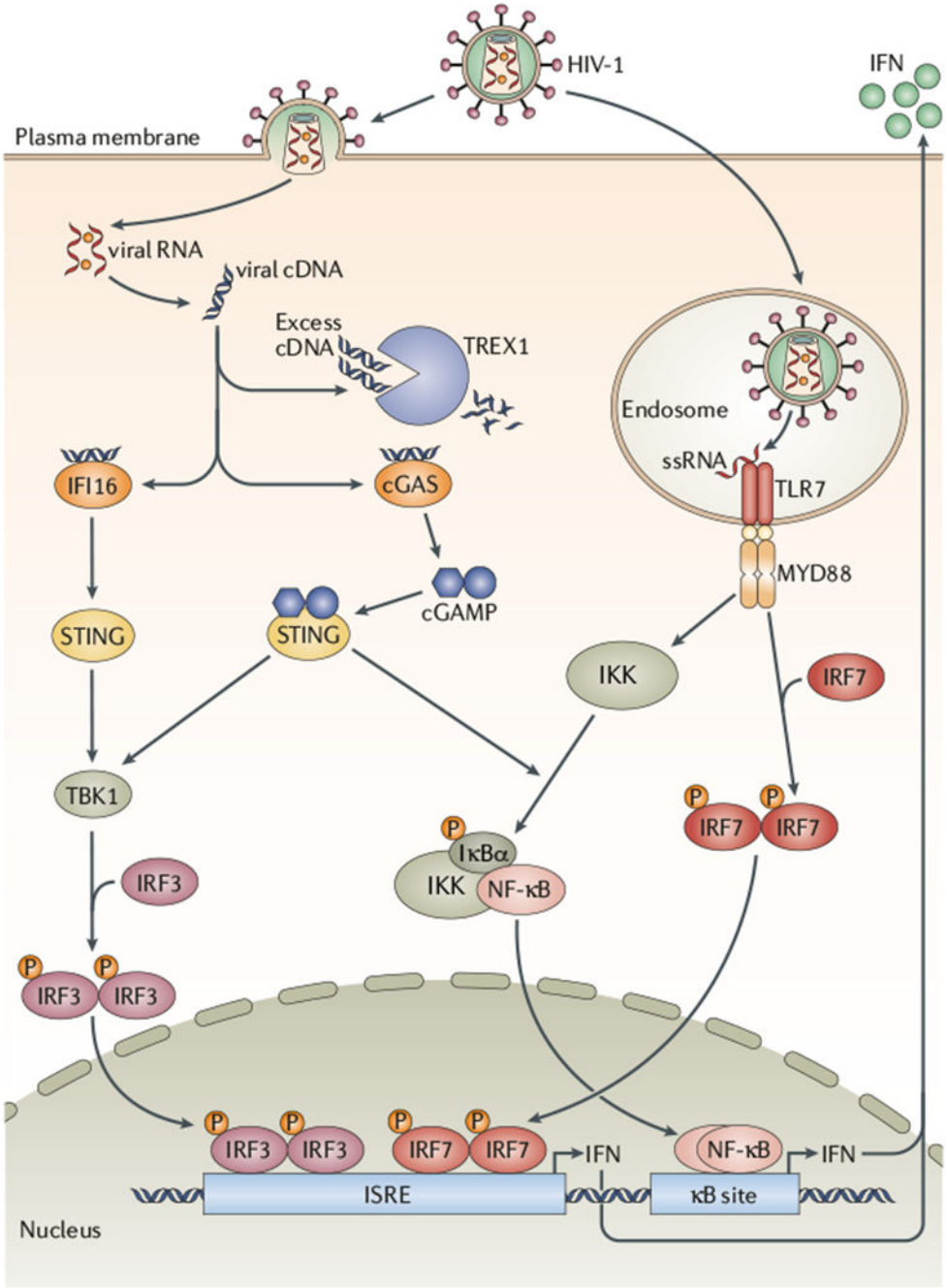

Figure 2 |. Intracellular sensing of HIV-1 Infection.

Following HIV-1 entry into the cell, viral RNA is reverse transcribed into cDNA, which is detected by the cytoplasmic receptors cyclic GMP–AMP (cGAMP) synthase (cGAS) and interferon-γ (IFNγ)-inducible protein 16 (IFI16). Following cDNA detection, IFI16 activates stimulator of IFN genes (STING), which leads to the activation of TANK-binding kinase 1 (TBK1) and the subseguent phosphorylation (P) of the IFN regulatory factor 3 (IRF3). Phosphorylated IRF3 can then engage IFN-stimulated response elements (ISREs), thereby inducing the expression of type I IFNs. When cGAS detects viral cDNA, the

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enzyme produces cGAMP, which leads to the activation of STING. STING then activates the inhibitor of NF-κB (IκB) kinase (IKK) complex and TBK1, leading to the activation of nuclear factor-κB (NF-κB) and IRF3, respectively. These transcription factors induce the expression of genes encoding IFNs and other pro-inflammatory cytokines. The cellular 3′-repair exonuclease 1 (TREX1) helps HIV-1 to evade cytosolic sensing by degrading viral cDNA in the cytoplasm. In addition to sensing cytoplasmic viral cDNA, cells can also sense HIV-1 single-stranded RNA (ssRNA) via Toll-like receptor 7 (TLR7) in endosomes, especially in plasmacytoid dendritic cells (pDCs). TLR7 activation by ssRNA in pDC endosomes results in the activation of myeloid differentiation primary response gene 88 (MYD88) and subseguent induction of IFN via activation of IRF7 and NF-κB.

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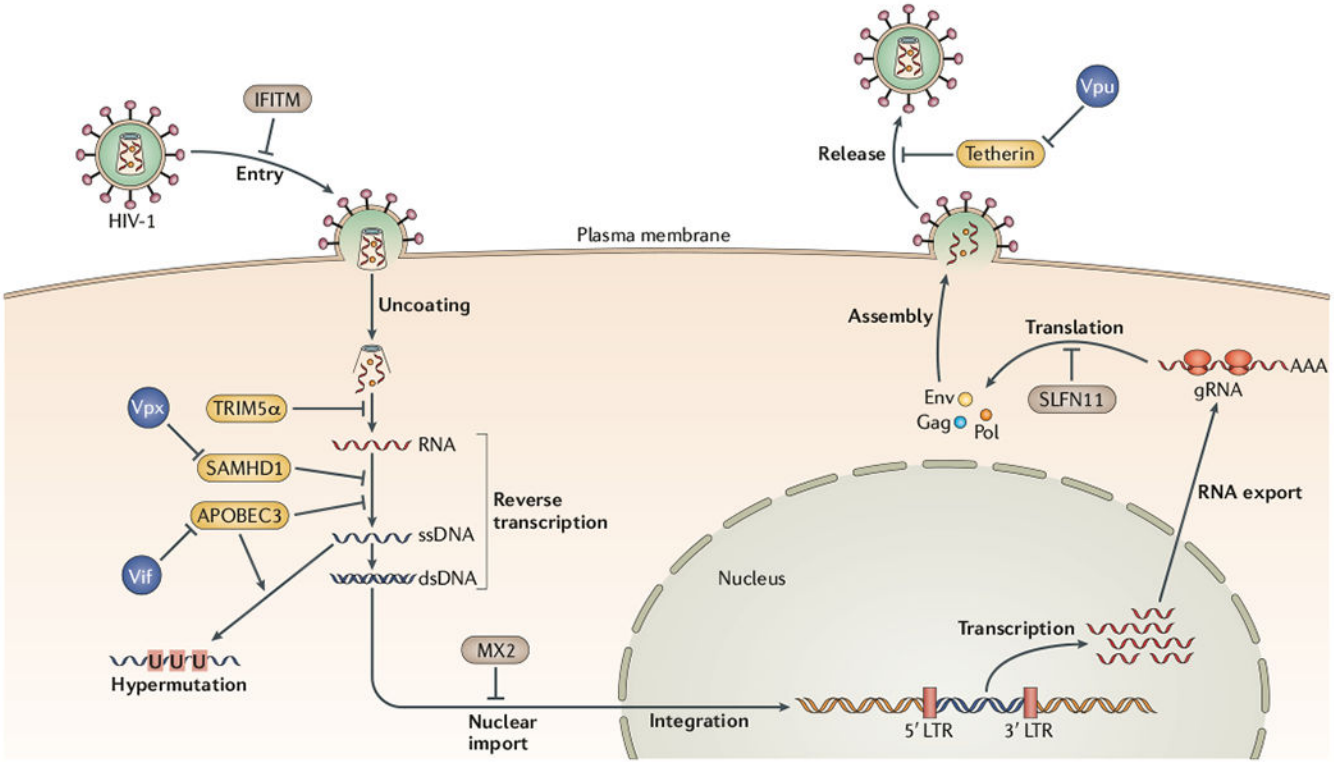

Figure 3 |. HIV-1 restriction and resistance factors.

In the absence of viraLLy encoded antagonists (or viral escape), host cell proteins called HIV-1 restriction factors (yellow) inhibit various stages of the replication cycle. The tripartite motif-containing protein 5α (TRIM5α) promotes accelerated fragmentation of viral cores, preventing cDNA synthesis. SAM and HD domain-containing protein 1 (SAMHD1) depletes the cellular levels of 2′-deoxynucleoside 5′-triphosphates (dNTPs), which are reguired for efficient cDNA synthesis. APOBEC3 (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3) proteins interfere with the processivity of HIV-1 reverse transcriptase and induce hypermutation of viral cDNA by cytidine deamination. Tetherin prevents the release of budded virions from the infected cell. Several viral proteins (blue) antagonize these cellular restriction factors. Viral infectivity factor (Vif) antagonizes APOBEC3 proteins, viral protein unique (Vpu) antagonizes tetherin, and the HIV-2 viral protein X (Vpx) antagonizes SAMHD1. HIV-1 resistance factors (brown) inhibit other stages of viral replication and are not counteracted by the virus. Myxovirus resistance 2 (MX2) prevents the nuclear import and integration of viral cDNA. Schlafen 11 (SLFN11) suppresses the translation of viral proteins. Interferon-induced transmembrane proteins (IFITMs) inhibit viral entry by interfering with membrane fusion. dsDNA, double-stranded DNA; gRNA, viral genomic RNA; LTR, long terminal repeat; ssDNA, single-stranded DNA.

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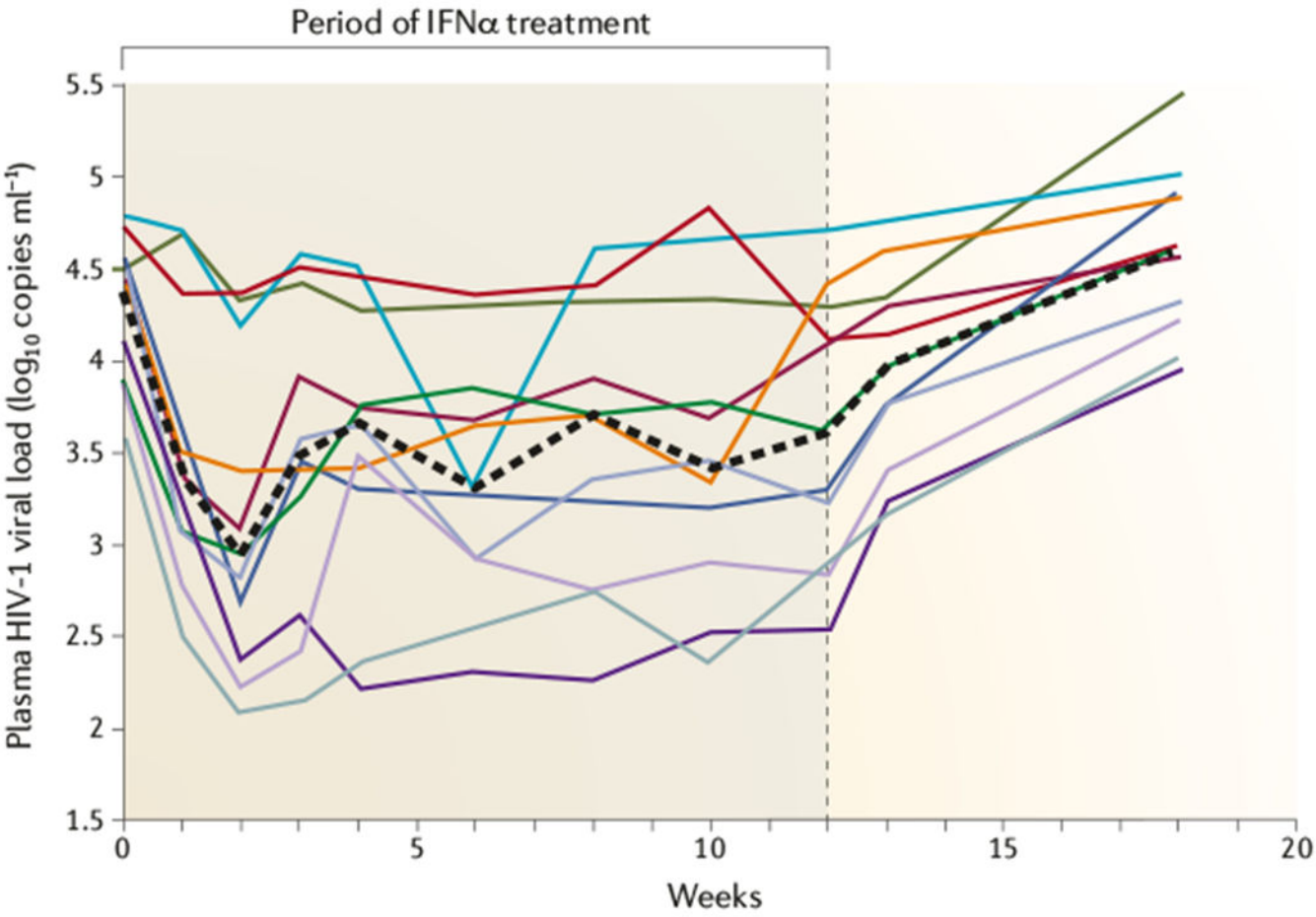

Figure 4 |. The effect of IFNα treatment on plasma HIV-1 viral load.

The graph shows plasma HIV-1 viral load (PVL) responses in patients who are infected with HIV-1 and who have not received antiretroviral therapy, during 12 weeks of treatment with pegylated-interferon-α (IFNα). The thick dashed line indicates the median PVL. IFNα treatment induces a rapid decline in PVL in most patients, whereas a minority fail to respond. The PVL reaches a nadir at 2 weeks (median reduction of 1.3 $\log_{10}$ copies ml^{-1} from baseline), followed by partial reversal of the response. Adapted from Asmuth, D. M. *et al.,* Safety, tolerability, and mechanisms of antiretroviral activity of pegylated interferon alfa-2a in HIV-l-monoinfected participants: a phase II clinical trial, *J. Infect. Dis.*, 2010, **201**, 11, 1686–1196, by permission of Oxford University Press.