



# The Effect of miRNA Gene Regulation on HIV Disease

Romona Chinniah<sup>1,2†</sup>, Theolan Adimulam<sup>2†</sup>, Louansha Nandlal<sup>1</sup>, Thilona Arumugam<sup>2</sup> and Veron Ramsuran<sup>1,2\*</sup>

<sup>1</sup>Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa,

<sup>2</sup>School of Laboratory Medicine and Medical Sciences, University of KwaZulu-Natal, Durban, South Africa

Over many years, research on HIV/AIDS has advanced with the introduction of HAART. Despite these advancements, significant gaps remain with respect to aspects in HIV life cycle, with specific attention to virus-host interactions. Investigating virus-host interactions may lead to the implementation of novel therapeutic strategies against HIV/AIDS. Notably, host gene silencing can be facilitated by cellular small non-coding RNAs such as microRNAs paving the way for epigenetic anti-viral therapies. Numerous studies have elucidated the importance of microRNAs in HIV pathogenesis. Some microRNAs can either promote viral infection, while others can be detrimental to viral replication. This is accomplished by targeting the HIV-proviral genome or by regulating host genes required for viral replication and immune responses. In this review, we report on 1) the direct association of microRNAs with HIV infection; 2) the indirect association of known human genetic factors with HIV infection; 3) the regulation of human genes by microRNAs in other diseases that can be explored experimentally to determine their effect on HIV-1 infection; and 4) therapeutic interactions of microRNA against HIV infection.

**Keywords:** microRNA, HIV, host-genetics, epigenetics, miRNA

## 1 INTRODUCTION

The Human Immunodeficiency Virus (HIV) is a member of the lentivirus family of retroviruses that infects humans and increases susceptibility to Acquired Immunodeficiency Syndrome (AIDS). At the end of 2020, more than 38 million people were living with HIV globally (Global, 2020). While an effective vaccine remains elusive, extensive research on the inhibition of various stages of the HIV life cycle has paved the way for the development of many antiretroviral drugs (Cohen et al., 2016). Despite the progress with lifesaving, highly active antiretroviral therapy (HAART), treatment may lead to the development of drug toxicities and resistance (Pomerantz and Horn, 2003). HAART has also been implicated in the onset of adverse metabolic effects such as dyslipidaemia, elevated blood pressure, and insulin resistance (Palios et al., 2011). These compounding factors emphasise the necessity for new less toxic, more effective and additional, complementary therapeutic approaches.

Advancements in discovering and determining the function of host factors in viral biogenesis and transmission highlight the possibility of developing new therapeutic tools for preventative measures and treatment of HIV/AIDS (Hoxie and June, 2012). As such, modulating gene expression post-transcriptionally using small non-coding RNAs (sncRNAs) mediates cellular gene silencing through RNA interference (RNAi). This mode of regulation has become increasingly utilized in the development and delivery of the therapeutic anti-viral strategy (Balasubramaniam et al., 2018). Eukaryotic cells possess endogenous RNAi mechanisms, of which microRNAs (miRNAs) are the most significant family of sncRNAs (Ghildiyal and Zamore, 2009). MiRNAs are a class of small non-

## OPEN ACCESS

### Edited by:

Gabriel Adelman Cipolla,  
Federal University of Paraná, Brazil

### Reviewed by:

Weizhong Chang,  
National Cancer Institute at Frederick  
(NIH), United States  
Shokrollah Elahi,  
University of Alberta, Canada

Shaheen Mowla,  
University of Cape Town, South Africa

### \*Correspondence:

Veron Ramsuran  
ramsuranv@ukzn.ac.za

<sup>†</sup>These authors have contributed  
equally to this work

### Specialty section:

This article was submitted to  
RNA,  
a section of the journal  
Frontiers in Genetics

**Received:** 26 January 2022

**Accepted:** 13 April 2022

**Published:** 04 May 2022

### Citation:

Chinniah R, Adimulam T, Nandlal L,  
Arumugam T and Ramsuran V (2022)  
The Effect of miRNA Gene Regulation  
on HIV Disease.  
Front. Genet. 13:862642.  
doi: 10.3389/fgene.2022.862642

coding RNA molecules (21–25 nucleotides in length) that are instrumental in regulating gene expression of multiple cellular processes, including differentiation, development, apoptosis, and stress response (Felekakis et al., 2010). These molecules exert their regulatory mechanisms by mRNA degradation or translational repression (prevention of translation of target mRNAs) (Cai et al., 2009; Fabian et al., 2010; Inui et al., 2010; Subramanian and Steer, 2010). The biogenesis of miRNAs is detailed profoundly in several manuscripts, which describe the two principal pathways (canonical and non-canonical) (O'Brien et al., 2018; Ha and Kim, 2014; Macfarlane and R. Murphy, 2010; Zhao et al., 2019).

Briefly, the canonical pathway begins in the nucleus where a primary RNA (pri-miRNA), usually ~80 nucleotides long, is transcribed from its specific gene by RNA polymerase II. The pri-miRNA is then cleaved to form a precursor miRNA (pre-miRNA), generally ~60 nucleotides long, by the Microprocessor complex (Zhao et al., 2019). The Microprocessor complex consists of two multiprotein units. The first is a large multiprotein unit. The second is a small multiprotein which constitutes of Drosha (RNase III enzyme) and the RNA binding protein DiGeorge Syndrome Critical Region 8 (DGCR8) (Gregory et al., 2004). Once the pre-miRNA is generated, it is transported to the cytoplasm by exportin-5 and Ran-GTP, where it undergoes cleavage by Dicer (O'Brien et al., 2018). The Dicer enzyme removes the terminal loop, thus resulting in a double-stranded product that consists of the mature miRNA guide strand and a passenger strand. The mature miRNA product will be transferred onto Argonaute (AGO) protein (Macfarlane and R. Murphy, 2010). The remaining passenger strands are usually directed toward degradation. However, the guide strand is further integrated into the RNA-induced silencing complex (RISC) (O'Brien et al., 2018; Macfarlane and R. Murphy, 2010). Finally, the RISC-miRNA complex principally binds to the 3'UTR of the target mRNA. The complementarity of this binding predicts the fate of the mRNA, such that, in the event of perfect complementarity, the target mRNA is degraded. However, when this binding is incomplete, the mRNA is translationally repressed (Cai et al., 2009).

Several non-canonical pathways have been described (Annese et al., 2020). In summary, non-canonical pathways are classified into Drosha/DGCR8-independent and Dicer-independent pathways. The class of Drosha/DGCR8-independent miRNAs which originate from spliced introns are commonly known as mirtrons. These miRNAs are instantly transported to the cytoplasm via Dicer processing (Treiber et al., 2019). On the contrary, Dicer-independent miRNAs are uncommon. Drosha processes Dicer-independent miRNAs from endogenous short hairpin RNA (shRNA) transcripts, directly recognised by Ago proteins, thus making them Dicer-independent (Dai et al., 2019).

Multiple studies have linked aberrant miRNA profiles to diseases such as cancer (Croce and Calin, 2005; Calin and Croce, 2006), neurodegenerative disease (Kim et al., 2007; Wang et al., 2008), autoimmune disease (Dai et al., 2007; Stanczyk et al., 2008; Zhao et al., 2010), inflammatory diseases (Sonkoly et al., 2007), muscular disorders (Eisenberg et al., 2007), cardiovascular disorders (Carè et al., 2007; Ikeda et al., 2007), in

addition to developmental abnormalities and psychiatric disorders (Lewis et al., 2003). Moreover, the five biggest infectious killers globally, including HIV/AIDS, are responsible for approximately 80% of the total contagious disease burden. About 12 million people per year succumb to these diseases, primarily in developing countries (Organization, 2020). Comparable to non-infectious conditions, miRNAs affect host and virus interactions in various ways. They are characterised as direct alteration of viral replication by influencing viral susceptibility or as indirect alteration of host genes that influence viral replication (Scaria et al., 2007; Kumar and Jeang, 2008).

MiRNAs have previously been implicated in HIV infection (Sun et al., 2016; Balasubramaniam et al., 2018; Su et al., 2018). As a field in its infancy, there is a substantial benefit in determining the impact of miRNAs on HIV infection.

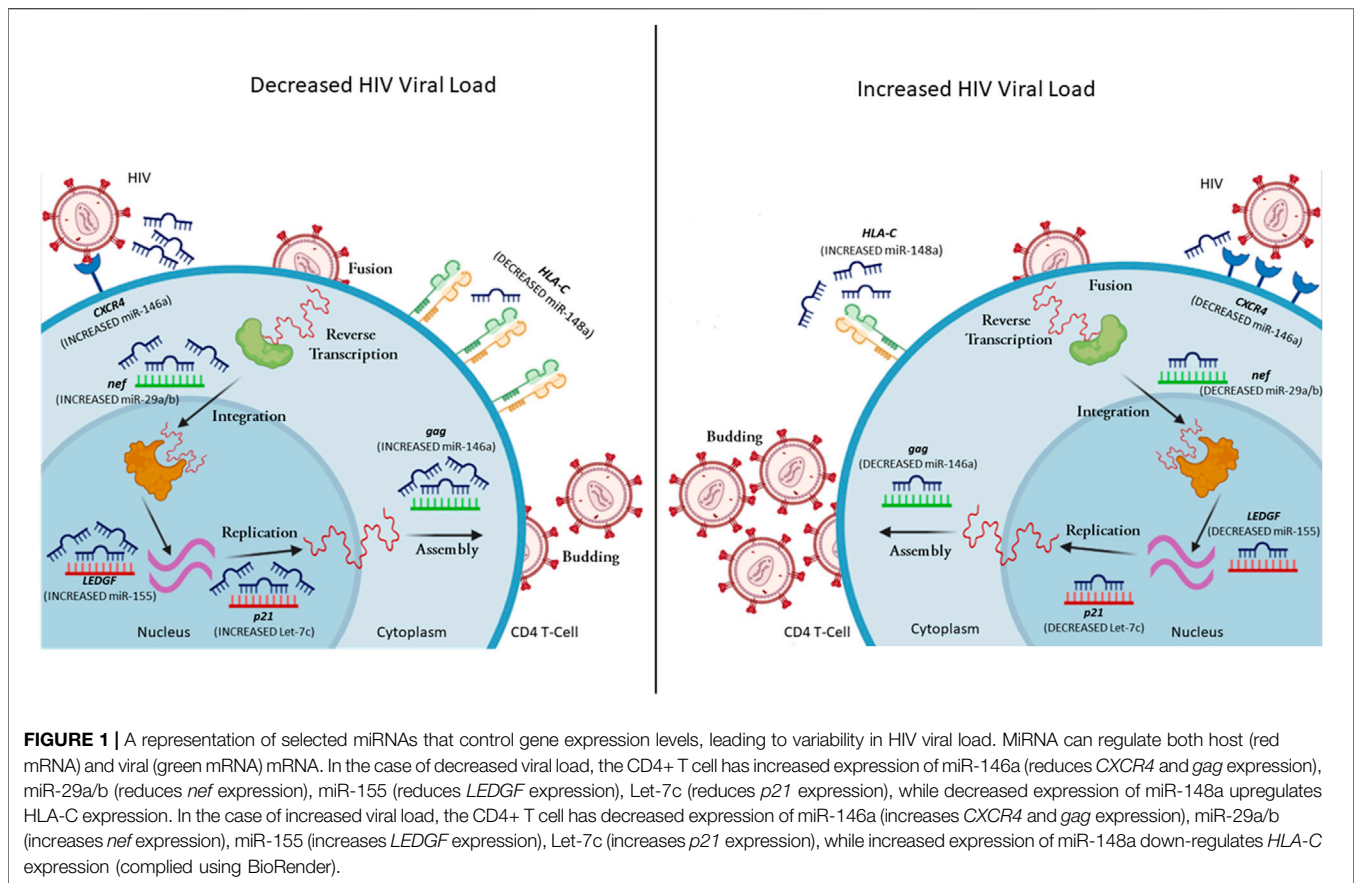
This review discusses the direct alterations of miRNAs in HIV infection and the indirect alterations of known human genetic factors in HIV infection. Thereafter, we describe miRNA associations of known human genetic factors with other diseases that can be exploited to determine their specific effect on HIV infection, and the potential use of miRNAs as therapeutic interactions against HIV infection.

## 2 EFFECT OF MIRNAS ON HIV INFECTION

MiRNAs can aid or obstruct HIV infection at various stages of the viral life cycle, affecting viral replication, host immune response, and ultimately disease management (**Figure 1**). HIV exploits and uses cellular miRNAs to modulate its replication by directly targeting its RNA or host mRNAs that would negatively impact HIV replication. In addition, miRNAs are linked with a possible susceptibility to HIV infection in monocytes and macrophages (Wang et al., 2009; Qiuling et al., 2018). Furthermore, the viral genome may produce viral encoded miRNAs that modulate viral RNAs as well as cellular mRNAs (Cullen, 2006; Skalsky and Cullen, 2010). This suggests that HIV could potentially regulate its replication cycle and possibly program its own latency (Omoto et al., 2004; Bennasser et al., 2006; Ouellet et al., 2013; Zhang et al., 2014). Several cellular miRNAs have demonstrated the ability to modulate HIV infection, either directly or indirectly (**Table 1**).

### 2.1 Regulation of HIV Replication Through Viral Genome

Host derived miRNAs can bind to HIV RNA, directly regulating pathogenesis (Trobaugh and Klimstra, 2017). For instance, recent data has shown that miR-139-5p plays a role in activating latent HIV infected cells, by regulating *FOXO1*, as well as *FOS* and *JUN* transcription factors (Okoye et al., 2021). The expression of miR-28, miR-125b, miR-150, miR-223, and miR-382 were significantly lower in activated CD4+ T cells in comparison to its resting counterpart. The same group of miRNAs may play a role in establishing viral latency by interacting with a conserved 1.2 kb fragment found in the 3'UTR of all HIV transcripts. These miRNAs



can inhibit the translation of all viral proteins with the exception of *nef* (Huang et al., 2007). Moreover, the study showed that infected cells with established latency could be reactivated by treatment with miRNA inhibitors, suggesting that cellular miRNAs may provide a mechanistic effect towards HIV latency (Huang et al., 2007). Besides their role in promoting HIV latency, these five miRNAs play a crucial role in preventing HIV infection of monocytes and monocyte-derived macrophages (MDM). MiR-28, miR-125b, miR-150, miR-223, and miR-382 were observed at significantly higher levels in monocytes compared to MDM. These miRNAs were found to impede HIV reverse transcriptase activity in both cell types. However, the activity of HIV reverse transcriptase was dependant on the level of these miRNAs. This may explain why monocyte differentiation into macrophages is required for effective HIV infection (Wang et al., 2009).

*Nef* expression can also be influenced by cellular miRNAs (Ahluwalia et al., 2008; Sun et al., 2012). Ahluwalia et al. found that miR-29a and miR-29b may target HIV *nef* expression, which resulted in repression of *nef* translation and subsequent decrease in viral load (Figure 1) (Ahluwalia et al., 2008).

Moreover, in a series of refined experiments, Sun et al. demonstrated a new regulatory circuit during HIV infection (Sun et al., 2012). The downregulation of the miR-29 family could be associated with *nef* up-regulation and apoptosis of CD4+ cells (Sun et al., 2012). In addition, previous studies showed that miR-29 inhibited HIV replication by approximately 60%, while

miR-133b, miR-138, miR-326, miR-149, and miR-92a reduced HIV viral replication by 40% (Houzet et al., 2012). In silico screening showed that these miRNAs may possibly target the 5'LTR (miR-326), *env* (miR-133b, miR-138), *gag* (miR-149), and *pol* (miR-92a) leading to the repression of viral replication.

Recent work by Chen et al. showed another form of miRNA regulation of HIV viruses through the interaction of miR-146a with the viral protein *gag* (Figure 1) (Chen et al., 2014). This interaction resulted in a viral-RNA-mediated *gag* assembly blockage, thereby interfering with viral budding and infectivity (Chen et al., 2014). These findings illustrate that miRNAs can alter viral gene expression via direct targeting of HIV mRNAs, with variable mechanisms of action dictated by the cell types.

## 2.2 Host Factors That Regulate HIV Replication

MiRNAs regulate HIV infection through indirect modulation of host factor expression. One viral-dependent factor in cells is Cyclin T1, characterised as an essential part of the PTEFb complex, responsible for facilitating viral transcription (Hoque et al., 2011). The direct modulation is facilitated through the interaction with *tat*, which recruits the complex to HIV TAR, thereby impacting viral latency (Hoque et al., 2011). Recent work by Sung et al. described that miR-198 targets and down-regulates Cyclin T1 mRNA and protein expression, which subsequently

**TABLE 1 |** Studies showing microRNAs affecting host cell genes in the context of HIV infection.

microRNA	Target	Action	Experimental approach/observation	References number
miR-148a	<i>HLA-C</i>	Impaired control of HIV viral load	<i>In vitro</i> studies Genetic association with HIV $P = 2 \times 10^{-14}$ , $R = 0.33$ , $N = 2.527$ (European cohort)	Kulkarni et al. (2011)
miR-146a	<i>CXCR4</i>	Prevents HIV entry	<i>In vitro</i>	Quaranta et al. (2015)
miR-132	<i>MeCP2</i>	Enhances HIV infection	<i>In vitro</i>	Chiang et al. (2013)
miR-182	<i>NAMPT</i>	Enhance HIV tat-mediated trans-activation	<i>In vitro</i>	Chen et al. (2013)
miR-34a miR-217	<i>SIRT1</i>	Enhances HIV tat mediated trans-activation	<i>In vitro In vitro</i>	Zhang et al. (2012a), Zhang et al. (2012b)
miR-34a	<i>PNUTS</i>	Promotes HIV -1 transcription	<i>In vitro</i>	Kapoor et al. (2015)
miR- 155	<i>TRIM32</i>	Promotes reactivation of latent HIV via NF- $\kappa$ B signalling	<i>In vitro</i>	Ruelas et al. (2015)
miR-17-5p miR-20a	<i>PCAF</i>	Reduction of HIV infection	<i>In vitro</i>	Triboulet et al. (2007)
miR-198 miR-27b	<i>Cyclin T1</i>	Impaired replication in monocytes	<i>In vitro In vitro</i>	Sung and Rice. (2009), Chiang et al. (2012)
miR-29b miR-150		Impaired HIV replication in resting CD4+ T cells		
miR-223				
miR-15a miR-15b	<i>Pur-Alpha</i>	Impaired HIV replication in monocytes	<i>In vitro</i>	Shen et al. (2012)
miR-16 miR-20a miR-93 miR-106b				
miR-155	<i>ADAM 10</i>	Reduction of HIV late RT products and viral DNA integration in MDM	<i>In vitro</i>	Swaminathan et al. (2012c)
miR-155	<i>NUP153</i>	Reduction of HIV late RT products and viral DNA integration in MDM	<i>In vitro</i>	Swaminathan et al. (2012c)
miR-155	<i>LEDGF/p75</i>	Reduction of HIV late RT products and viral DNA integration in MDM	<i>In vitro</i>	Swaminathan et al. (2012c)
miR-155 miR-181	<i>SAMHD1</i>	Overexpression of miR-155/181a enhanced HIV replication in astrocytes	<i>In vitro</i>	Pilakka-Kanthikeel et al. (2015)
miR1236	<i>VprBP</i>	Impaired HIV replication in monocytes	<i>In vitro</i>	Ma et al. (2014)
let-7c	<i>p21</i>	Increased HIV replication	<i>In vitro</i>	Farberov et al. (2015)
miR-124a miR34a-5p	<i>TASK1</i>	Increased HIV replication	<i>In vitro</i>	Farberov et al. (2015)
miR-146a	<i>CCL5</i>	Enhance HIV infection	<i>In vitro</i>	Qiuling et al. (2018)
miR-21	<i>IP-10</i>	miR-21 expression downregulates IP-10 controlling the loss of CD4+ T cells which is closely related to disease progression	Genetic association in HIV disease $p < 0.0001$ , $R = 0.706$ , $N = 32$ (Chinese cohort)	Wu et al. (2017)
miR-155	<i>PU.1 (DC-SIGN)</i>	Reduces HIV entry into T lymphocytes	<i>In vitro</i>	Martinez-Nunez et al. (2009)
miR-9	<i>BLIMP-1</i>	Reduced HIV infection	<i>Ex vivo and in vitro</i>	Seddiki et al. (2013)
let-7	<i>IL-10</i>	Reduced HIV infection	<i>Ex vivo and in vitro</i>	Swaminathan et al. (2012c)
miR-221 miR-222	<i>CD4</i>	Inhibition of HIV entry in macrophages	<i>In vitro</i>	Lodge et al. (2017)
miR-34c-5p	Several genes are involved in TCR signaling and activation of naïve CD4+ T cells	Increased HIV replication	<i>In vitro</i>	Amaral et al. (2017)
miR-29a miR-29b miR-29c	<i>IL-32</i>	Proviral load and disease progression	Genetic association in HIV disease $p = 0.079$ , $R = 0.232$ , $N = 58$ $p = 0.102$ , $R = 0.445$ , $N = 58$ $p = 0.103$ , $R = 0.216$ , $N = 58$	Monteleone et al. (2015)

Notes: *P* represents the *p* value for the specific result. *R* represents the value of the statistical Pearson *R*. *N* is representative of the number of samples. The italic values under the "Target" column is indicative of gene names. While the italic values under the "Experimental approach/observation" is the Latin caption used to define how the experiment was performed.

impairs the *tat*-mediated transcriptional activation of HIV in infected monocytes and macrophages (Sung and Rice, 2009). Over-expression of miR-198 inhibited HIV replication in macrophages, suggesting that cell type-specific mechanisms may be an effect executed by miRNAs (Sung and Rice, 2009). Additional studies identified that Cyclin T1 inhibition is exerted by cellular miRNAs (miR-27b, miR-29b, miR-150, and miR-223) in resting CD4+ T cells (Chiang et al., 2012). However, CD4+ T cell activation followed the downregulation of the miRNAs. This result was correlated with enhanced HIV susceptibility and productive replication (Chiang et al., 2012).

The viral protein *tat* is an essential transcriptional activator that interacts with several cellular proteins. For efficient HIV transcriptional activation, *tat* must be acetylated by p300-CREB binding protein associated factor (PCAF) (D'Orso and Frankel, 2009). Remarkably, miR-17/92 family of host miRNAs impedes HIV infection by downregulating PCAF (Triboulet et al., 2007). Triboulet *et al.* also showed that miR-17 as well as miR-20a inhibited PCAF expression at the mRNA and protein levels. In addition, HIV can actively repress miR-17-5p and miR-20a to enhance viral translation through p300/PCAF-dependant *tat* activation (Triboulet et al., 2007).

Another well characterised cellular factor that interacts with HIV *tat* to up-regulate viral transcription is the purine-rich element binding protein  $\alpha$  (Pur- $\alpha$ ) (Wortman et al., 2000). A collection of six cellular miRNAs (miR-15a, miR-15b, miR-16, miR-20a, miR-93, and miR-106b) enriched in monocytes were linked with the repression of Pur- $\alpha$  (Shen et al., 2012). Consequently, inhibition of these miRNAs in monocytes increased the expression of Pur- $\alpha$ , resulting in an increase in HIV infection (Shen et al., 2012).

MiR-155 has demonstrated significant effects on HIV infection through a Toll-Like receptor (TLR)-dependant mechanism (Swaminathan et al., 2012a). Swaminathan *et al.* showed that miR-155 is significantly up-regulated in MDMs, stimulated by TLR3 and TLR4 (Swaminathan et al., 2012a). Furthermore, up-regulation of miR-155 through TLR stimulation leads to decreased mRNA and protein expression of ADAM10, TNPO3, NUP153, and LEDGF/p75, in MDMs (Swaminathan et al., 2012a). Gene silencing of *LEDGF* had the most significant effect on HIV infection (**Figure 1**) (Swaminathan et al., 2012a). However, co-silencing of both *LEDGF* and *ADAM10* had a more substantial impact, impairing the transport of viral pre-integration complexes (Swaminathan et al., 2012a).

The inhibition of *TRIM32* by miR-155 results in post-integration latency of HIV (Ruelas et al., 2015). *TRIM32* directs NF- $\kappa$ B to the nucleus via a *tat*-independent mechanism, as described by Ruelas et al. (2015). The study characterises a novel mechanism by which *TRIM32* activates NF- $\kappa$ B. Collectively, the inhibitory effect of miR-155 on *TRIM32* highlights a new tool for HIV remaining in infected reservoirs (Ruelas et al., 2015). Despite this significant study, recent studies have identified miR-155 as a potent biomarker of activated T cells and immune dysfunction in HIV-infected individuals (Jin et al., 2017a; Jin et al., 2017b; Zhang et al., 2021a).

MiRNAs can also restrict viral entry by targeting the receptors and co-receptors exploited for HIV entry. Orecchini *et al.* report a *tat*-dependant mechanism that controls CD4 receptor by up-regulating miR-222 (Orecchini et al., 2014). In addition, Lodge *et al.* demonstrated that miR-221 and miR-222 are up-regulated in MDMs, targeting the 3' UTR of CD4 (Orecchini et al., 2014). The mRNA and subsequent protein expression are reduced, ultimately impairing HIV entry into MDM (Lodge et al., 2017). Labbaye *et al.* showed that promyelocytic leukaemia zinc finger (PLZF) could regulate miR-146a, subsequently controlling the expression of *CXCR4* *in vitro* (Labbaye et al., 2008). Activation of resting CD4+ T cells by phytohemagglutinin results in the downregulation of miR-146a (Quaranta et al., 2015). Downregulation of miR-146a results in the overexpression of *CXCR4* co-receptor promoting viral entry in CD4+ T cells (Quaranta et al., 2015).

Vpr HIV-binding protein (vprBP) is a cellular cofactor that forms part of a ubiquitin protein ligase complex. VprBP promotes HIV infection (Ma et al., 2014). Ma *et al.* demonstrated that miR-1236 inhibitors increased translation of vprBP in monocytes, thus facilitating HIV infection. Contrary to monocytes, miR-1236 mimics in monocyte-derived dendritic cells had suppressed vprBP, which was complemented by decreased infection (Ma et al., 2014).

High surface expression of human leukocyte antigen C (HLA-C) greatly corresponded with slower disease progression via superior control of HIV viremia. Several genetic variants have been shown to disrupt miR-148a regulation of HLA-C (Kulkarni et al., 2011; Blais et al., 2012; Kulkarni et al., 2013). Disruption of miRNA binding site allows high expressing HLA-C alleles to escape miR-148a regulation (Kulkarni et al., 2011). HLA-C alleles that do not have a disrupted miR-148a binding site are tightly regulated by miR-148a and are expressed at low levels. The polymorphisms affecting HLA-C expression through disrupted miR-148a binding are rs9264942, rs67384697, and rs735316, with the variants of rs9264942 and rs67384697 being in linkage disequilibrium (Kulkarni et al., 2011; Blais et al., 2012; Kulkarni et al., 2013). All three variants are associated with control and progression of HIV infection by miR-148a-mediated post-transcriptional regulation of HLA-C.

IL-10 is a multifunctional anti-inflammatory cytokine produced by various immune cells. With regards to miRNA regulation of IL-10, the let-7 family can directly target *IL10*. *In vitro* infection with HIV elevated *IL10* levels through the reduction of let-7. In addition, CD4+ T cells of chronically infected HIV-positive individuals had significantly lower let-7 levels than uninfected individuals and long-term non-progressors. (Swaminathan et al., 2012b). A single miRNA is able to regulate multiple target genes. In addition to *IL10*, let-7c is involved in the regulation of *p21*. let-7c overexpression in Jurkat cells resulted in a 1.38-fold change in *p21* expression (**Figure 1**) (Farberov et al., 2015).

B lymphocyte-induced maturation protein-1 (Blimp-1) is a transcriptional repressor of IL-2 (an important cytokine required for T cell growth and survival). In HIV-infected individuals, BLIMP-1 may contribute to T cell dysregulation through alterations in IL-2 levels. MiR-9 inhibited *BLIMP1* expression in CD4+ T cells. Chronically infected HIV-positive patients had lower miR-9 and higher *BLIMP1* expression in comparison to uninfected healthy individuals and long-term non-progressors (Seddiki et al., 2013).

## 2.3 Predicted miRNA Targets for HIV

It is estimated that 1,254 human genes are involved in viral replication. Genome-wide RNA interference has enabled researchers to identify multiple host factors that are involved in HIV life cycle. This large array of host gene targets may be essential in the development of new therapeutic strategies against HIV. By identifying and understanding the mechanisms behind the associations of specific miRNAs and their targets, we can exploit these factors for HIV viral control. Several HIV-associated genes are shown to be under the regulation of miRNAs in other diseases.

Blocking the access of HIV into host cells is the first step in preventing the HIV proviral genome from integrating into the host's genome. The human chemokine receptor 5 (CCR5) plays an important role in the internalization of HIV into the host cell (Lederman et al., 2006). Individuals with the 32 base pair deletion in their *CCR5* gene are known to be resistant to HIV as they have lower levels of CCR5 on the surface of their CD4+ T cells. Thus, the regulation of CCR5 expression

may be essential in inhibiting HIV replication. Che *et al.* found that miR-107 binds to the 3'UTR of *CCR5* (Che *et al.*, 2016). *CCR5* proteins and gene expression were found to be significantly lower in the presence of miR-107 (Che *et al.*, 2016). Since *CCR5* is important in the HIV context, miR-107 may be of potential therapeutic value in preventing HIV infection.

Intercellular adhesion molecule 1 (ICAM-1) also plays a significant role in HIV entry. The binding of ICAM-1 with LFA-1 on the cell surface facilitates viral infectivity. ICAM-1 increases viral infectivity by directly inserting into mature HIV virions (Fortin *et al.*, 1997; Bounou *et al.*, 2002). Lui *et al.* demonstrated that *ICAM1* is negatively regulated by miR-296-3p in the malignant highly metastatic M12 cell line (Liu *et al.*, 2013). Furthermore, in prostate cancer cells there is a negative correlation between miR-296-3p and *ICAM1* (Liu *et al.*, 2013). In the context of HIV, the downregulation of *ICAM1* by miR-296-3p would reduce the rate of infectivity (Liu *et al.*, 2013).

The tripartite motif (TRIM) proteins are a family of E3 ubiquitin ligases with diverse anti-viral functions (van Gent *et al.*, 2018). TRIM22, TRIM11, and KAP1 (TRIM28) were previously shown to have anti-HIV activity (Barr *et al.*, 2008; Allouch *et al.*, 2009; Yuan *et al.*, 2016). TRIM22 inhibits the processing of viral particles and viral budding through the ubiquitylation in HIV. TRIM22 also has anti-Hepatitis C virus (HCV) activity. Tian *et al.* confirmed that *TRIM22* was regulated by miR-215 (Tian and He, 2018). In Con1b cells, the overexpression of miR-215 facilitated HCV replication by downregulating *TRIM22*. Knockdown of miR-215 suppressed HCV replication through the increased expression of *TRIM22* in Huh7.5.1 cells (Tian and He, 2018). In colon cancer, *TRIM11* is negatively regulated by miR-24-3p, promoting cellular proliferation and inhibiting apoptosis (Yin *et al.*, 2016). Likewise, Qi *et al.* demonstrated that miR-491 levels inversely corresponded with *TRIM28* expression in glioblastoma multiforme (GBM) (Qi *et al.*, 2016). Their data showed that miR-491 was reduced in GBM and indicated that the low levels of miR-491 are associated with poor prognosis (Qi *et al.*, 2016). miR-491 inhibited *TRIM28* translation in GBM cells (Qi *et al.*, 2016).

Studies have also demonstrated a link between *RAD51* expression and HIV disease (Chipitsyna *et al.*, 2004; Cosnefroy *et al.*, 2012; Kaminski *et al.*, 2014; Thierry *et al.*, 2015). Elevated expression of *RAD51* promotes HIV-1 transcription (Kaminski *et al.*, 2014). Evidence demonstrates that *RAD51* may have stimulatory or inhibitory effects on specific steps of retroviral replication cycles (Thierry *et al.*, 2015). These effects depend on *RAD51* being able to recruit both transcription machinery and proteins implicated in chromatin remodelling and formulation of *RAD51* stimulatory compound (Thierry *et al.*, 2015). Findings from Gasparini *et al.* indicate that DNA repair is indirectly regulated by miR-155 through its interaction with *RAD51* in breast cancer (Gasparini *et al.*, 2014).

The regulation of several other HIV-associated host factors such as TRAF6, CCL4, CCL3, IRF7, RSAD2, ISG15, TLR3,

SETDB1, and Rab27a by miRNAs could potentially play a role in HIV infection. **Table 2** provides a list of HIV-associated host genes which should be investigated in future miRNA studies. The host's genes and associated miRNAs described in **Table 2** may provide novel therapeutic targets against HIV.

## 2.4 Therapeutic miRNA Targets for HIV

Extensive research has paved the way for developing multiple antiretroviral drugs targeting specific phases of the viral life cycle, leading to a combination of antiretroviral therapy (cART). Currently, this treatment results in controlled viral replication in many treated individuals (Cohen *et al.*, 2016). Despite the progress with lifesaving HAART, infection with HIV remains pathogenic and incurable. In addition, these drugs lead to the development of toxicities and adverse side effects which may only be combated by changing the drug regimen. Furthermore, the increasing emergence of HIV drug resistance poses a threat to the success of the current regimens (Bertagnolli *et al.*, 2012; Le Douce *et al.*, 2012; Stadeli and Richman, 2013). These compounding factors highlight the importance of identifying novel and complementary treatment regimens.

RNA-based therapeutics appear ready to deliver on their promise. Significant success has been observed in several clinical trials using potential miRNA drugs in multiple infectious and non-infectious diseases, including cancer (Hatley *et al.*, 2010; Li *et al.*, 2010; Steele *et al.*, 2011; Wong *et al.*, 2012; Yamanaka *et al.*, 2012), hepatitis C (Jopling *et al.*, 2005; Sarasin-Filipowicz *et al.*, 2009; Lanford *et al.*, 2010), heart abnormalities (Thum *et al.*, 2008; Liu *et al.*, 2010), kidney disease, pathologic fibrosis, and even keloid formation. Interestingly, studies have also shown that dysregulated miRNA profiles play a role in HIV replication (Barr *et al.*, 2008; Pincetic *et al.*, 2010; Liu *et al.*, 2011; Sirois *et al.*, 2011; Tyagi and Kashanchi, 2012; Raposo *et al.*, 2013; Doyle *et al.*, 2015). The vaccine, iHIVARNA is a combination of mRNA sequences that serve as an HIV immunogen. In the first round of clinical trials, iHIVARNA is tolerated in HIV-infected patients on chronic cART (De Jong *et al.*, 2019). Despite this progress, the application of miRNAs as diagnostic and interventional medicine remains an underexplored area of research. The clinical trial was merely a proof-of-concept trial; the stability and delivery of the mRNA are still being tested (De Jong *et al.*, 2019).

The Achilles heel of miRNA-based viral therapy is the lack of targeted miRNA delivery systems, off-target effects, and unidentified targets of miRNAs. In addition, miRNAs are relatively unstable, which may result in insufficient circulation and poor half-life of the miRNA-based therapy. Future research should be directed towards constructing optimal miRNA delivery systems and identifying methods to prevent off-target effects. As the use of miRNAs as treatment strategies is a growing field, only a few drugs have been FDA approved (Nature Biotechnology, 2020; Zhang *et al.*, 2021b), which highlights the potential of RNAs for therapeutic intervention. MiRNAs provide a unique, reversible approach to treating human diseases and may be our secret weapon in our fight against HIV.

**TABLE 2 |** Genes associated with HIV infection shown to be regulated by miRNAs in other diseases.

HIV infection			Other disease		
Gene	Effect	References number	microRNA	Disease or infection	References number
Viral receptors					
<i>CCR5</i>	responsible for HIV infection and entry	Blanpain et al. (2002); Lederman et al. (2006)	miR-107	Cancer	Che et al. (2016)
<i>ICAM-1</i>	assists with HIV entry increasing virus infectivity	Fortin et al., (1997); Bounou et al. (2002)	miR-296-3p	Prostate cancer	Liu et al. (2013)
Innate immune regulators					
<i>TRIM22</i>	blocks HIV replication in cell by preventing the assembly of the virus	Barr et al. (2008)	miR-215	HCV	Tian and He, (2018)
<i>TRIM28 (KAP1)</i>	inhibits HIV-1 through by targeting the integration step	Allouch et al. (2009)	miR-149	Cancer	Qi et al. (2016)
<i>TRIM11</i>	restricts HIV-1 reverse transcription by accelerating viral un-coating	Yuan et al. (2016)	miR-24-3p	Colon cancer	Yin et al. (2016)
<i>TRAF6</i>	induced as part of the normal innate immune response against HIV virus	Sirois et al. (2011)	miR-146a miR-144	Dengue virus influenza virus, EMCV, and VSV	Wu et al. (2013) Rosenberger et al. (2017)
T cell exhaustion markers					
<i>CCL4</i>	CCR5 ligand involved in blocking HIV entry	Carrol et al. (1999)	miR-125b	Aging	Cheng et al. (2015)
<i>CCL3</i>	CCR5 ligand involved in blocking HIV entry	Modi et al., (2006); Levine et al., (2009)	miR-223	Tuberculosis	Dorhoi et al. (2013)
<i>IRF7</i>	contributes to enhanced HIV-1 replication	Sirois et al. (2011)	miR-541	Vascular smooth muscle cells	Yang et al. (2016)
<i>RSAD2 (viperin)</i>	Inhibits viral production	Raposo et al. (2013)	miR-200a miR-200b miR-429	Cell differentiation studies	Li et al. (2016)
<i>ISG15</i>	Suppresses HIV replication at various parts of the HIV life cycle	Pincetic et al. (2010); Doyle et al., (2015)	miR-138 miR-370	Oral cancer	Zhang et al. (2017)
Toll-like receptors					
<i>TLR3</i>	Innate immune response. Reduces HIV infection	Akira et al., (2006); Swaminathan et al. (2012c)	miR-26a	Arthritis	Jiang et al. (2014)
Other					
<i>RAD51</i>	stimulatory or inhibitory effects on specific steps on retroviral replication cycles	(Kaminski et al., 2014; Thierry et al., 2015)	miR-155	Cancer	Gasparini et al. (2014)
<i>SETDB1</i>	Inhibits HIV-1 replication at a step prior to integration	(Liu et al., 2011; Tyagi and Kashanchi, 2012)	miR-381-3p	Breast cancer	Wu et al. (2018)
<i>Rab27a</i>	Favours HIV assembly	Gerber et al. (2015)	miR-134-3p	Ovarian cancer	Chang et al. (2017)

Notes: HCV, abbreviates Hepatitis C. EMCV, abbreviates encephalomyocarditis virus; VSV, abbreviates vesicular stomatitis virus.

### 3 CONCLUSION

MiRNAs play a significant role in regulating gene expression. While the role of miRNAs in diseases such as cancer has been thoroughly investigated, the interplay between miRNAs and HIV infection has only begun to emerge. MiRNAs have emerged as key contributors to immune dysfunction observed in HIV disease. As research develops in specific subsets and more targeted populations, the understanding of this field matures as more can be uncovered. Considering that key genes involved in the HIV life cycle are affected by differentially expressed miRNAs, there is a link between the host's RNA interference machinery and HIV pathogenicity. Future research should focus on identifying differentially expressed miRNAs in HIV-infected

donors from different population groups., which may be exploited for therapeutic benefit.

In addition, the application of specific miRNA mimics and inhibitors (Andorfer et al., 2011; He et al., 2012; De Santa et al., 2013) is an appealing avenue for future investigations. Noting that one miRNA alone may be able to target several host genetic factors, the combined effect of several miRNAs together offers the potential for a multi-targeted effect. This treatment strategy can complement current cART regimen. Furthermore, inhibition of selected miRNAs is advantageous. For instance, selectively blocking miRNAs that target anti-viral proteins or pathways could potentially enhance anti-viral responses. This approach is efficient during the onset of infection, as the anti-viral response to HIV can be improved.

## AUTHOR CONTRIBUTIONS

Conceptualization and conceiving of idea, VR. Additional input with regards to conceptualization, RC. Writing, RC, TA, TAR, and LN. Research, RC, TA, TAR, and LN. Figure design, TA and VR. Editing of manuscript, VR. All authors contributed to the article and approved the submitted version.

## FUNDING

VR was funded as a FLAIR Research Fellow (the Future Leader in African Independent Research (FLAIR) Fellowship Programme was a partnership between the African Academy of Sciences (AAS) and the Royal Society that was

funded by the UK Government as part of the Global Challenge Research Fund (GCRF) Grant # FLAIR-FLR\1\190204); supported by the South African Medical Research Council (SAMRC) with funds from the Department of Science and Technology (DST); and VR was also supported in part through the Sub-Saharan African Network for TB/HIV Research Excellence (SANTHE), a DELTAS Africa Initiative (Grant # DEL-15-006) by the AAS. TA is funded by the Poliomyelitis Research Foundation (PRF) Grant # 21/49.

## ACKNOWLEDGMENTS

In Memoriam of the late author Romona Chinniah.

## REFERENCES

- Ahluwalia, J. K., Khan, S. Z., Soni, K., Rawat, P., Gupta, A., Hariharan, M., et al. (2008). Human Cellular microRNA Hsa-miR-29a Interferes with Viral Nef Protein Expression and HIV-1 Replication. *Retrovirology* 5, 117. doi:10.1186/1742-4690-5-117
- Akira, S., Uematsu, S., and Takeuchi, O. (2006). Pathogen Recognition and Innate Immunity. *Cell* 124 (4), 783–801. doi:10.1016/j.cell.2006.02.015
- Allouch, A., et al. (2009). HIV-1 Acetylated Integrase Is Targeted by KAP1 (TRIM28) to Inhibit Viral Integration. *Retrovirology* 6 (Suppl. 2), P2. doi:10.1186/1742-4690-6-s2-p2
- Amaral, A. J., Andrade, J., Foxall, R. B., Matoso, P., Matos, A. M., Soares, R. S., et al. (2017). Mi RNA Profiling of Human Naive CD 4 T Cells Links miR-34c-5p to Cell Activation and HIV Replication. *Embo j* 36 (3), 346–360. doi:10.15252/embj.201694335
- Andorfer, C. A., Necela, B. M., Thompson, E. A., and Perez, E. A. (2011). MicroRNA Signatures: Clinical Biomarkers for the Diagnosis and Treatment of Breast Cancer. *Trends Mol. Med.* 17 (6), 313–319. doi:10.1016/j.molmed.2011.01.006
- Annese, T., Tamma, R., De Giorgis, M., and Ribatti, D. (2020). microRNAs Biogenesis, Functions and Role in Tumor Angiogenesis. *Front. Oncol.* 10, 581007. doi:10.3389/fonc.2020.581007
- Balasubramaniam, M., Pandhare, J., and Dash, C. (2018). Are microRNAs Important Players in HIV-1 Infection? an Update. *Viruses* 10 (3), 110. doi:10.3390/v10030110
- Barr, S. D., Smiley, J. R., and Bushman, F. D. (2008). The Interferon Response Inhibits HIV Particle Production by Induction of TRIM22. *Plos Pathog.* 4 (2), e1000007-e1000007. doi:10.1371/journal.ppat.1000007
- Bennasser, Y., Bennasser, Y., Le, S. Y., Yeung, M. L., and Jeang, K. T. (2006). MicroRNAs in Human Immunodeficiency Virus-1 Infection. *Methods Mol Biol* 342, 241–253. doi:10.1385/1-59745-123-1:241
- Bertagnolio, S., De Luca, A., Vitoria, M., Essajee, S., Penazzato, M., Hong, S. Y., et al. (2012). Determinants of HIV Drug Resistance and Public Health Implications in Low- and Middle-Income Countries. *Antivir. Ther.* 17 (6), 941–953. doi:10.3851/imp2320
- Blais, M.-E., Zhang, Y., Rostron, T., Griffin, H., Taylor, S., Xu, K., et al. (2012). High Frequency of HIV Mutations Associated with HLA-C Suggests Enhanced HLA-C-Restricted CTL Selective Pressure Associated with an AIDS-Protective Polymorphism. *J.I.* 188 (9), 4663–4670. doi:10.4049/jimmunol.1103472
- Blanpain, C., Libert, F., Vassart, G., and Parmentier, M. (2002). CCR5 and HIV Infection. *Receptors and Channels* 8 (1), 19–31. doi:10.3109/10606820212135
- Bounou, S., Leclerc, J. E., and Tremblay, M. J. (2002). Presence of Host ICAM-1 in Laboratory and Clinical Strains of Human Immunodeficiency Virus Type 1 Increases Virus Infectivity and CD4 + T-Cell Depletion in Human Lymphoid Tissue, a Major Site of Replication *In Vivo*. *J. Virol.* 76 (3), 1004–1014. doi:10.1128/jvi.76.3.1004-1014.2002
- Cai, Y., Yu, X., Hu, S., and Yu, J. (2009). A Brief Review on the Mechanisms of miRNA Regulation. *Genomics, proteomics & bioinformatics* 7 (4), 147–154. doi:10.1016/s1672-0229(08)60044-3
- Calin, G. A., and Croce, C. M. (2006). MicroRNA Signatures in Human Cancers. *Nat. Rev. Cancer* 6 (11), 857–866. doi:10.1038/nrc1997
- Carè, A., Catalucci, D., Felicetti, F., Bonci, D., Addario, A., Gallo, P., et al. (2007). MicroRNA-133 Controls Cardiac Hypertrophy. *Nat. Med.* 13 (5), 613–618. doi:10.1038/nm1582
- Carroll, E. D., Mankambo, L. A., Balmer, P., Nkhoma, S., Banda, D. L., Guiver, M., et al. (1999). Chemokine Responses Are Increased in HIV-Infected Malawian Children with Invasive Pneumococcal Disease. *J. Acquir Immune Defic Syndr.* 44 (4), 443–450. doi:10.1097/QAI.0b013e31802f8390
- Chang, C., Liu, T., Huang, Y., Qin, W., Yang, H., and Chen, J. (2017). MicroRNA-134-3p Is a Novel Potential Inhibitor of Human Ovarian Cancer Stem Cells by Targeting RAB27A. *Gene* 605, 99–107. doi:10.1016/j.gene.2016.12.030
- Che, L.-F., Shao, S.-F., and Wang, L.-X. (2016). Downregulation of CCR5 Inhibits the Proliferation and Invasion of Cervical Cancer Cells and Is Regulated by microRNA-107. *Exp. Ther. Med.* 11 (2), 503–509. doi:10.3892/etm.2015.2911
- Chen, A. K., Sengupta, P., Waki, K., Van Engelenburg, S. B., Ochiya, T., Ablan, S. D., et al. (2014). MicroRNA Binding to the HIV-1 Gag Protein Inhibits Gag Assembly and Virus Production. *Proc. Natl. Acad. Sci. U S A.* 111 (26), E2676–E2683. doi:10.1073/pnas.1408037111
- Chen, X.-Y., Zhang, H.-S., Wu, T.-C., Sang, W.-W., and Ruan, Z. (2013). Downregulation of NAMPT Expression by miR-182 Is Involved in Tat-Induced HIV-1 Long Terminal Repeat (LTR) Transactivation. *Int. J. Biochem. Cell Biol.* 45 (2), 292–298. doi:10.1016/j.biocel.2012.11.002
- Cheng, N. L., Chen, X., Kim, J., Shi, A. H., Nguyen, C., Wersto, R., et al. (2015). MicroRNA-125b Modulates Inflammatory Chemokine CCL4 Expression in Immune Cells and its Reduction Causes CCL4 Increase with Age. *Aging cell* 14 (2), 200–208. doi:10.1111/acer.12294
- Chiang, K., Liu, H., and Rice, A. P. (2013). miR-132 Enhances HIV-1 Replication. *Virology* 438 (1), 1–4. doi:10.1016/j.virol.2012.12.016
- Chiang, K., Sung, T.-L., and Rice, A. P. (2012). Regulation of Cyclin T1 and HIV-1 Replication by MicroRNAs in Resting CD4 + T Lymphocytes. *J. Virol.* 86 (6), 3244–3252. doi:10.1128/jvi.05065-11
- Chipitsyna, G., Slonina, D., Siddiqui, K., Peruzzi, F., Skorski, T., Reiss, K., et al. (2004). HIV-1 Tat Increases Cell Survival in Response to Cisplatin by Stimulating Rad51 Gene Expression. *Oncogene* 23 (15), 2664–2671. doi:10.1038/sj.onc.1207417
- Cohen, M. S., Chen, Y. Q., McCauley, M., Gamble, T., Hosseinipour, M. C., Kumarasamy, N., et al. (2016). Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *N. Engl. J. Med.* 375 (9), 830–839. doi:10.1056/NEJMoa1600693
- Cosnefroy, O., Tocco, A., Lesbats, P., Thierry, S., Calmels, C., Wiktorowicz, T., et al. (2012). Stimulation of the Human RAD51 Nucleofilament Restricts HIV-1 Integration *In Vitro* and in Infected Cells. *J. Virol.* 86 (1), 513–526. doi:10.1128/jvi.05425-11
- Croce, C. M., and Calin, G. A. (2005). miRNAs, Cancer, and Stem Cell Division. *Cell* 122 (1), 6–7. doi:10.1016/j.cell.2005.06.036
- Cullen, B. R. (2006). Viruses and microRNAs. *Nat. Genet.* 38 Suppl (6), S25–S30. doi:10.1038/ngl793
- D'Orso, I., and Frankel, A. D. (2009). Tat Acetylation Modulates Assembly of a Viral-Host RNA-Protein Transcription Complex. *Proc. Natl. Acad. Sci. U.S.A.* 106 (9), 3101–3106. doi:10.1073/pnas.0900012106



- Dai, X., Kaushik, A. C., and Zhang, J. (2019). The Emerging Role of Major Regulatory RNAs in Cancer Control. *Front. Oncol.* 9, 920. doi:10.3389/fonc.2019.00920
- Dai, Y., Huang, Y.-S., Tang, M., Lv, T.-Y., Hu, C.-X., Tan, Y.-H., et al. (2007). Microarray Analysis of microRNA Expression in Peripheral Blood Cells of Systemic Lupus Erythematosus Patients. *Lupus* 16 (12), 939–946. doi:10.1177/0961203307084158
- De Jong, W., Aerts, J., Allard, S., Brander, C., Buyze, J., Florence, E., et al. (2019). iHIVARNA Phase IIa, a Randomized, Placebo-Controlled, Double-Blinded Trial to Evaluate the Safety and Immunogenicity of iHIVARNA-01 in Chronically HIV-Infected Patients under Stable Combined Antiretroviral Therapy. *Trials* 20 (1), 361–410. doi:10.1186/s13063-019-3409-1
- De Santa, F., Iosue, I., and Fazi, F. (2013). microRNA Biogenesis Pathway as a Therapeutic Target for Human Disease and Cancer. *Curr. Pharm. Des.* 19, 745–764. doi:10.2174/138161213804581846
- Dorhoi, A., Iannaccone, M., Farinacci, M., Faé, K. C., Schreiber, J., Moura-Alves, P., et al. (2013). MicroRNA-223 Controls Susceptibility to Tuberculosis by Regulating Lung Neutrophil Recruitment. *J. Clin. Invest.* 123 (11), 4836–4848. doi:10.1172/jci67604
- Doyle, T., Goujon, C., and Malim, M. H. (2015). HIV-1 and Interferons: Who's Interfering with Whom? *Nat. Rev. Microbiol.* 13 (7), 403–413. doi:10.1038/nrmicro3449
- Eisenberg, I., Eran, A., Nishino, I., Moggio, M., Lamperti, C., Amato, A. A., et al. (2007). Distinctive Patterns of microRNA Expression in Primary Muscular Disorders. *Proc. Natl. Acad. Sci. U.S.A.* 104 (43), 17016–17021. doi:10.1073/pnas.0708115104
- Fabian, M. R., Sonenberg, N., and Filipowicz, W. (2010). Regulation of mRNA Translation and Stability by microRNAs. *Annu. Rev. Biochem.* 79, 351–379. doi:10.1146/annurev-biochem-060308-103103
- Farberov, L., Herzig, E., Modai, S., Isakov, O., Hizi, A., and Shomron, N. (2015). MicroRNA-mediated Regulation of P21 and TASK1 Cellular Restriction Factors Enhances HIV-1 Infection. *J. Cell Sci.* 128 (8), 1607–1616. doi:10.1242/jcs.167817
- Felekis, K., Touvana, E., Stefanou, C. h., and Deltas, C. (2010). microRNAs: a Newly Described Class of Encoded Molecules that Play a Role in Health and Disease. *Hippokratia* 14 (4), 236–240.
- Fortin, J. F., Cantin, R., Lamontagne, G., and Tremblay, M. (1997). Host-derived ICAM-1 Glycoproteins Incorporated on Human Immunodeficiency Virus Type 1 Are Biologically Active and Enhance Viral Infectivity. *J. Virol.* 71 (5), 3588–3596. doi:10.1128/jvi.71.5.3588-3596.1997
- Gasparini, P., Lovat, F., Fassin, M., Casadei, L., Cascione, L., Jacob, N. K., et al. (2014). Protective Role of miR-155 in Breast Cancer through RAD51 Targeting Impairs Homologous Recombination after Irradiation. *Proc. Natl. Acad. Sci. U.S.A.* 111 (12), 4536–4541. doi:10.1073/pnas.1402604111
- Gerber, P. P., Cabrini, M., Jancic, C., Paoletti, L., Banchio, C., von Bilderling, C., et al. (2015). Rab27a Controls HIV-1 Assembly by Regulating Plasma Membrane Levels of Phosphatidylinositol 4,5-bisphosphate. *J. Cell Biol.* 209 (3), 435–452. doi:10.1083/jcb.201409082
- Ghildiyal, M., and Zamore, P. D. (2009). Small Silencing RNAs: an Expanding Universe. *Nat. Rev. Genet.* 10 (2), 94–108. doi:10.1038/nrg2504
- Global, U. N. A. I. D. S. (2020). HIV & AIDS Statistics — Fact Sheet. Available at: <https://www.unaids.org/en/resources/fact-sheet>.
- Gregory, R. I., Yan, K.-p., Amuthan, G., Chendrimada, T., Doratotaj, B., Cooch, N., et al. (2004). The Microprocessor Complex Mediates the Genesis of microRNAs. *Nature* 432 (7014), 235–240. doi:10.1038/nature03120
- Ha, M., and Kim, V. N. (2014). Regulation of microRNA Biogenesis. *Nat. Rev. Mol. Cell Biol.* 15 (8), 509–524. doi:10.1038/nrm3838
- Hatley, M. E., Patrick, D. M., Garcia, M. R., Richardson, J. A., Bassel-Duby, R., van Rooij, E., et al. (2010). Modulation of K-ras-dependent Lung Tumorigenesis by MicroRNA-21. *Cancer cell* 18 (3), 282–293. doi:10.1016/j.ccr.2010.08.013
- He, M.-L., Luo, M. X.-M., Lin, M. C., and Kung, H.-f. (2012). MicroRNAs: Potential Diagnostic Markers and Therapeutic Targets for EBV-Associated Nasopharyngeal Carcinoma. *Biochim. Biophys. Acta (Bba) - Rev. Cancer* 1825 (1), 1–10. doi:10.1016/j.bbcan.2011.09.001
- Hoque, M., Shamanna, R. A., Guan, D., Pe'ery, T., and Mathews, M. B. (2011). HIV-1 Replication and Latency Are Regulated by Translational Control of Cyclin T1. *J. Mol. Biol.* 410 (5), 917–932. doi:10.1016/j.jmb.2011.03.060
- Houzet, L., Klase, Z., Yeung, M. L., Wu, A., Le, S.-Y., Quiñones, M., et al. (2012). The Extent of Sequence Complementarity Correlates with the Potency of Cellular miRNA-Mediated Restriction of HIV-1. *Nucleic Acids Res.* 40 (22), 11684–11696. doi:10.1093/nar/gks912
- Hoxie, J. A., and June, C. H. (2012). Novel Cell and Gene Therapies for HIV. *Cold Spring Harbor Perspect. Med.* 2 (10), a007179. doi:10.1101/cshperspect.a007179
- Huang, J., Wang, F., Argyris, E., Chen, K., Liang, Z., Tian, H., et al. (2007). Cellular microRNAs Contribute to HIV-1 Latency in Resting Primary CD4+ T Lymphocytes. *Nat. Med.* 13 (10), 1241–1247. doi:10.1038/nm1639
- Ikeda, S., Kong, S. W., Lu, J., Bisping, E., Zhang, H., Allen, P. D., et al. (2007). Altered microRNA Expression in Human Heart Disease. *Physiol. genomics* 31 (3), 367–373. doi:10.1152/physiolgenomics.00144.2007
- Inui, M., Martello, G., and Piccolo, S. (2010). MicroRNA Control of Signal Transduction. *Nat. Rev. Mol. Cell Biol.* 11 (4), 252–263. doi:10.1038/nrm2868
- Jiang, C., Zhu, W., Xu, J., Wang, B., Hou, W., Zhang, R., et al. (2014). MicroRNA-26a Negatively Regulates Toll-like Receptor 3 Expression of Rat Macrophages and Ameliorates Pristane Induced Arthritis in Rats. *Arthritis Res. Ther.* 16 (1), R9. doi:10.1186/ar4435
- Jin, C., Cheng, L., Höxtermann, S., Xie, T., Lu, X., Wu, H., et al. (2017). MicroRNA-155 Is a Biomarker of T-Cell Activation and Immune Dysfunction in HIV-1-Infected Patients. *HIV Med.* 18 (5), 354–362. doi:10.1111/hiv.12470
- Jin, C., Cheng, L., Lu, X., Xie, T., Wu, H., and Wu, N. (2017). Elevated Expression of miR-155 Is Associated with the Differentiation of CD8+ T Cells in Patients with HIV-1. *Mol. Med. Rep.* 16 (2), 1584–1589. doi:10.3892/mmr.2017.6755
- Jopling, C. L., Yi, M., Lancaster, A. M., Lemon, S. M., and Sarnow, P. (2005). Modulation of Hepatitis C Virus RNA Abundance by a Liver-specific MicroRNA. *science* 309 (5740), 1577–1581. doi:10.1126/science.1113329
- Kaminski, R., Wollebo, H. S., Datta, P. K., White, M. K., Amini, S., and Khalili, K. (2014). Interplay of Rad51 with NF-Kb Pathway Stimulates Expression of HIV-1. *PLoS ONE* 9, e98304. doi:10.1371/journal.pone.0098304
- Kapoor, R., Arora, S., Ponia, S. S., Kumar, B., Maddika, S., and Banerjee, A. C. (2015). The miRNA miR-34a Enhances HIV-1 Replication by Targeting PNUMS/PPP1R10, Which Negatively Regulates HIV-1 Transcriptional Complex Formation. *Biochem. J.* 470 (3), 293–302. doi:10.1042/bj20150700
- Kim, J., Inoue, K., Ishii, J., Vanti, W. B., Voronov, S. V., Murchison, E., et al. (2007). A MicroRNA Feedback Circuit in Midbrain Dopamine Neurons. *Science* 317 (5842), 1220–1224. doi:10.1126/science.1140481
- Kulkarni, S., Qi, Y., O'hUigin, C., Pereyra, F., Ramsuran, V., McLaren, P., et al. (2013). Genetic Interplay between HLA-C and MIR148A in HIV Control and Crohn Disease. *Proc. Natl. Acad. Sci. U.S.A.* 110 (51), 20705–20710. doi:10.1073/pnas.1312237110
- Kulkarni, S., Savan, R., Qi, Y., Gao, X., Yuki, Y., Bass, S. E., et al. (2011). Differential microRNA Regulation of HLA-C Expression and its Association with HIV Control. *Nature* 472 (7344), 495–498. doi:10.1038/nature09914
- Kumar, A., and Jeang, K.-T. (2008). Insights into Cellular microRNAs and Human Immunodeficiency Virus Type 1 (HIV-1). *J. Cell. Physiol.* 216 (2), 327–331. doi:10.1002/jcp.21488
- Labbaye, C., Spinello, I., Quaranta, M. T., Pelosi, E., Pasquini, L., Petrucci, E., et al. (2008). A Three-step Pathway Comprising PLZF/miR-146a/CXCR4 Controls Megakaryopoiesis. *Nat. Cell Biol.* 10 (7), 788–801. doi:10.1038/ncb1741
- Lanford, R. E., Hildebrandt-Eriksen, E. S., Petri, A., Persson, R., Lindow, M., Munk, M. E., et al. (2010). Therapeutic Silencing of microRNA-122 in Primates with Chronic Hepatitis C Virus Infection. *Science* 327 (5962), 198–201. doi:10.1126/science.1178178
- Le Douce, V., Janossy, A., Hallay, H., Ali, S., Riclet, R., Rohr, O., et al. (2012). Achieving a Cure for HIV Infection: Do We Have Reasons to Be Optimistic? *J. Antimicrob. Chemother.* 67 (5), 1063–1074. doi:10.1093/jac/dkr599
- Lederman, M. M., Penn-Nicholson, A., Cho, M., and Mosier, D. (2006). Biology of CCR5 and its Role in HIV Infection and Treatment. *Jama* 296 (7), 815–826. doi:10.1001/jama.296.7.815
- Levine, A., et al. (2009). CCL3 Genotype and Current Depression Increase Risk of HIV-Associated Dementia. *Neurobehav HIV Med.* Vol. 1, 1–7. doi:10.2147/nbhiv.s6820
- Lewis, B. P., Shih, I.-h., Jones-Rhoades, M. W., Bartel, D. P., and Burge, C. B. (2003). Prediction of Mammalian microRNA Targets. *Cell* 115 (7), 787–798. doi:10.1016/s0092-8674(03)01018-3
- Li, Y., Zhu, X., Gu, J., Hu, H., Dong, D., Yao, J., et al. (2010). Anti-miR-21 Oligonucleotide Enhances Chemosensitivity of Leukemic HL60 Cells to

- Arabinosylcytosine by Inducing Apoptosis. *Hematology* 15 (4), 215–221. doi:10.1179/102453310x12647083620840
- Li, Z., Yin, H., Hao, S., Wang, L., Gao, J., Tan, X., et al. (2016). miR-200 Family Promotes Podocyte Differentiation through Repression of RSAD2. *Sci. Rep.* 6, 27105. doi:10.1038/srep27105
- Liu, G., Friggeri, A., Yang, Y., Milosevic, J., Ding, Q., Thannickal, V. J., et al. (2010). miR-21 Mediates Fibrogenic Activation of Pulmonary Fibroblasts and Lung Fibrosis. *J. Exp. Med.* 207 (8), 1589–1597. doi:10.1084/jem.20100035
- Liu, L., Oliveira, N. M., Cheney, K. M., Pade, C., Dreja, H., Bergin, A.-M. H., et al. (2011). A Whole Genome Screen for HIV Restriction Factors. *Retrovirology* 8, 94. doi:10.1186/1742-4690-8-94
- Liu, X., Chen, Q., Yan, J., Wang, Y., Zhu, C., Chen, C., et al. (2013). MiRNA-296-3p-ICAM-1 axis Promotes Metastasis of Prostate Cancer by Possible Enhancing Survival of Natural Killer Cell-Resistant Circulating Tumour Cells. *Cell Death Dis* 4, e928. doi:10.1038/cddis.2013.458
- Lodge, R., Ferreira Barbosa, J. A., Lombard-Vadnais, F., Gilmore, J. C., Deshiere, A., Gosselin, A., et al. (2017). Host MicroRNAs-221 and -222 Inhibit HIV-1 Entry in Macrophages by Targeting the CD4 Viral Receptor. *Cel Rep.* 21 (1), 141–153. doi:10.1016/j.celrep.2017.09.030
- Ma, L., Shen, C.-J., Cohen, É. A., Xiong, S.-D., and Wang, J.-H. (2014). miRNA-1236 Inhibits HIV-1 Infection of Monocytes by Repressing Translation of Cellular Factor VprBP. *PLoS one* 9 (6), e99535. doi:10.1371/journal.pone.0099535
- Macfarlane, L.-A., and R. Murphy, P. (2010). MicroRNA: Biogenesis, Function and Role in Cancer. *Curr. Genomics* 11 (7), 537–561. doi:10.2174/138920210793175895
- Martinez-Nunez, R. T., Louafi, F., Friedmann, P. S., and Sanchez-Elsner, T. (2009). MicroRNA-155 Modulates the Pathogen Binding Ability of Dendritic Cells (DCs) by Down-Regulation of DC-specific Intercellular Adhesion Molecule-3 Grabbing Non-integrin (DC-SIGN). *J. Biol. Chem.* 284 (24), 16334–16342. doi:10.1074/jbc.m109.011601
- Modi, W. S., Lautenberger, J., An, P., Scott, K., Goedert, J. J., Kirk, G. D., et al. (2006). Genetic Variation in the CCL18-CCL3-CCL4 Chemokine Gene Cluster Influences HIV Type 1 Transmission and AIDS Disease Progression. *Am. J. Hum. Genet.* 79 (1), 120–128. doi:10.1086/505331
- Monteleone, K., Selvaggi, C., Cacciotti, G., Falasca, F., Mezzaroma, I., D'Ettorre, G., et al. (2015). MicroRNA-29 Family Expression and its Relation to Antiviral Immune Response and Viro-Immunological Markers in HIV-1-Infected Patients. *BMC Infect. Dis.* 15, 51. doi:10.1186/s12879-015-0768-4
- Nature Biotechnology (2020). Second RNAi Drug Approved. *Nat. Biotechnol.* 38, 385. doi:10.1038/s41587-020-0494-3
- O'Brien, J., Hayder, H., Zayed, Y., and Peng, C. (2018). Overview of microRNA Biogenesis, Mechanisms of Actions, and Circulation. *Front. Endocrinol.* 9, 402. doi:10.3389/fendo.2018.00402
- Okoye, I., Xu, L., Oyegbami, O., Shahbaz, S., Pink, D., Gao, P., et al. (2021). Plasma Extracellular Vesicles Enhance HIV-1 Infection of Activated CD4<sup>+</sup> T Cells and Promote the Activation of Latently Infected J-Lat10.6 Cells via miR-139-5p Transfer. *Front. Immunol.* 12, 697604. doi:10.3389/fimmu.2021.697604
- Omoto, S., Ito, M., Tsutsumi, Y., Ichikawa, Y., Okuyama, H., Brisibe, E. A., et al. (2004). HIV-1 Nef Suppression by Virally Encoded microRNA. *Retrovirology* 1 (1), 44–12. doi:10.1186/1742-4690-1-44
- Orecchini, E., Doria, M., Michienzi, A., Giuliani, E., Vassena, L., Ciafrè, S. A., et al. (2014). The HIV-1 Tat Protein Modulates CD4 Expression in Human T Cells through the Induction of miR-222. *RNA Biol.* 11 (4), 334–338. doi:10.4161/rna.28372
- Organization, W. H. (2020). Global Health Estimates 2016: Disease burden by Cause, Age, Sex, by Country and by Region, 2000–2016, 2018. *Geneva. Recuperado de* 390, 10100.
- Ouellet, D. L., Vigneault-Edwards, J., Létourneau, K., Gobeil, L. A., Plante, I., Burnett, J. C., et al. (2013). Regulation of Host Gene Expression by HIV-1 TAR microRNAs. *Retrovirology* 10 (1), 86–15. doi:10.1186/1742-4690-10-86
- Palios, J., Kadoglou, N. P., and Lampropoulos, S. (2011). *The Pathophysiology of HIV-/HAART-Related Metabolic Syndrome Leading to Cardiovascular Disorders: The Emerging Role of Adipokines*. Experimental Diabetes Research. Pilakka-Kanthikeel, S., Raymond, A., Atluri, V. S. R., Sagar, V., Saxena, S. K., Diaz, P., et al. (2015). Sterile Alpha Motif and Histidine/aspartic Acid Domain-Containing Protein 1 (SAMHD1)-Facilitated HIV Restriction in Astrocytes Is Regulated by miRNA-181a. *J. Neuroinflammation* 12, 66. doi:10.1186/s12974-015-0285-9
- Pincetic, A., Kuang, Z., Seo, E. J., and Leis, J. (2010). The Interferon-Induced Gene ISG15 Blocks Retrovirus Release from Cells Late in the Budding Process. *J. Virol.* 84 (9), 4725–4736. doi:10.1128/jvi.02478-09
- Pomerantz, R. J., and Horn, D. L. (2003). Twenty Years of Therapy for HIV-1 Infection. *Nat. Med.* 9 (7), 867–873. doi:10.1038/nm0703-867
- Qi, Z., Cai, S., Cai, J., Chen, L., Yao, Y., Chen, L., et al. (2016). miR-491 Regulates Glioma Cells Proliferation by Targeting TRIM28 *In Vitro*. *BMC Neurol.* 16 (1), 248. doi:10.1186/s12883-016-0769-y
- Qiuling, H., Chen, L., Luo, M., Lv, H., Luo, D., Li, T., et al. (2018). HIV-1-Induced miR-146a Attenuates Monocyte Migration by Targeting CCL5 in Human Primary Macrophages. *AIDS Res. Hum. Retroviruses* 34 (7), 580–589. doi:10.1089/AID.2017.0217
- Quaranta, M. T., Olivetta, E., Sanchez, M., Spinello, I., Paolillo, R., Arenaccio, C., et al. (2015). miR-146a Controls CXCR4 Expression in a Pathway that Involves PLZF and Can Be Used to Inhibit HIV-1 Infection of CD4<sup>+</sup> T Lymphocytes. *Virology* 478, 27–38. doi:10.1016/j.viro.2015.01.016
- Raposo, R. A. S., Abdel-Mohsen, M., Bilksa, M., Montefiori, D. C., Nixon, D. F., and Pillai, S. K. (2013). Effects of Cellular Activation on Anti-HIV-1 Restriction Factor Expression Profile in Primary Cells. *J. Virol.* 87 (21), 11924–11929. doi:10.1128/jvi.02128-13
- Rosenberger, C. M., Podyminogin, R. L., Diercks, A. H., Treuting, P. M., Peschon, J. J., Rodriguez, D., et al. (2017). miR-144 Attenuates the Host Response to Influenza Virus by Targeting the TRAF6-IRF7 Signaling axis. *Plos Pathog.* 13 (4), e1006305. doi:10.1371/journal.ppat.1006305
- Ruelas, D. S., Chan, J. K., Oh, E., Heidersbach, A. J., Hebbeler, A. M., Chavez, L., et al. (2015). MicroRNA-155 Reinforces HIV Latency. *J. Biol. Chem.* 290 (22), 13736–13748. doi:10.1074/jbc.m115.641837
- Sarasin-Filipowicz, M., Krol, J., Markiewicz, I., Heim, M. H., and Filipowicz, W. (2009). Decreased Levels of microRNA miR-122 in Individuals with Hepatitis C Responding Poorly to Interferon Therapy. *Nat. Med.* 15 (1), 31–33. doi:10.1038/nm.1902
- Scaria, V., Hariharan, M., Pillai, B., Maiti, S., and Brahmachari, S. K. (2007). Host-virus Genome Interactions: Macro Roles for microRNAs. *Cell Microbiol.* 9 (12), 2784–2794. doi:10.1111/j.1462-5822.2007.01050.x
- Seddiki, N., Phetsouphanh, C., Swaminathan, S., Xu, Y., Rao, S., Li, J., et al. (2013). The microRNA-9/b-Lymphocyte-Induced Maturation protein-1/IL-2 axis Is Differentially Regulated in Progressive HIV Infection. *Eur. J. Immunol.* 43 (2), 510–520. doi:10.1002/eji.201242695
- Shen, C. J., Jia, Y. H., Tian, R. R., Ding, M., Zhang, C., and Wang, J. H. (2012). Translation of Pur-α Is Targeted by Cellular miRNAs to Modulate the Differentiation-dependent Susceptibility of Monocytes to HIV-1 Infection. *FASEB J.* 26 (11), 4755–4764. doi:10.1096/fj.12-209023
- Sirois, M., Robitaille, L., Allary, R., Shah, M., Woelk, C. H., Estaquier, J., et al. (2011). TRAF6 and IRF7 Control HIV Replication in Macrophages. *PLOS ONE* 6 (11), e28125. doi:10.1371/journal.pone.0028125
- Skalsky, R. L., and Cullen, B. R. (2010). Viruses, microRNAs, and Host Interactions. *Annu. Rev. Microbiol.* 64, 123–141. doi:10.1146/annurev.micro.112408.134243
- Sonkoly, E., Wei, T., Janson, P. C. J., Sääf, A., Lundeberg, L., Tengvall-Linder, M., et al. (2007). MicroRNAs: Novel Regulators Involved in the Pathogenesis of Psoriasis? *PLoS one* 2 (7), e610. doi:10.1371/journal.pone.0000610
- Stadel, K. M., and Richman, D. D. (2013). Rates of Emergence of HIV Drug Resistance in Resource-Limited Settings: a Systematic Review. *Antivir. Ther.* 18 (1), 115–123. doi:10.3851/IMP2437
- Stanczyk, J., Pedrioli, D. M. L., Brentano, F., Sanchez-Pernaute, O., Kolling, C., Gay, R. E., et al. (2008). Altered Expression of MicroRNA in Synovial Fibroblasts and Synovial Tissue in Rheumatoid Arthritis. *Arthritis Rheum.* 58 (4), 1001–1009. doi:10.1002/art.23386
- Steele, C. W., Oien, K. A., McKay, C. J., and Jamieson, N. B. (2011). Clinical Potential of microRNAs in Pancreatic Ductal Adenocarcinoma. *Pancreas* 40 (8), 1165–1171. doi:10.1097/mpa.0b013e3182218fbb
- Su, B., Fu, Y., Liu, Y., Wu, H., Ma, P., Zeng, W., et al. (2018). Potential Application of microRNA Profiling to the Diagnosis and Prognosis of HIV-1 Infection. *Front. Microbiol.* 9, 3185. doi:10.3389/fmicb.2018.03185
- Subramanian, S., and Steer, C. J. (2010). MicroRNAs as Gatekeepers of Apoptosis. *J. Cell Physiol* 223 (2), 289–298. doi:10.1002/jcp.22066

- Sun, B., Yang, R., and Mallardo, M. (2016). Roles of microRNAs in HIV-1 Replication and Latency. *Mirna* 5 (2), 120–123. doi:10.2174/2211536605666160829123118
- Sun, G., Li, H., Wu, X., Covarrubias, M., Scherer, L., Meinking, K., et al. (2012). Interplay between HIV-1 Infection and Host microRNAs. *Nucleic Acids Res.* 40 (5), 2181–2196. doi:10.1093/nar/gkr961
- Sung, T.-L., and Rice, A. P. (2009). miR-198 Inhibits HIV-1 Gene Expression and Replication in Monocytes and its Mechanism of Action Appears to Involve Repression of Cyclin T1. *Plos Pathog.* 5 (1), e1000263. doi:10.1371/journal.ppat.1000263
- Swaminathan, G., Rossi, F., Sierra, L. J., Gupta, A., Navas-Martín, S., and Martín-García, J. (2012). A Role for microRNA-155 Modulation in the Anti-HIV-1 Effects of Toll-like Receptor 3 Stimulation in Macrophages. *PLoS Pathogens* 8 (9), e1002937. doi:10.1371/journal.ppat.1002937
- Swaminathan, G., Rossi, F., Sierra, L.-J., Gupta, A., Navas-Martín, S., and Martín-García, J. (2012). A Role for microRNA-155 Modulation in the Anti-HIV-1 Effects of Toll-like Receptor 3 Stimulation in Macrophages. *Plos Pathog.* 8 (9), e1002937. doi:10.1371/journal.ppat.1002937
- Swaminathan, S., Suzuki, K., Seddiki, N., Kaplan, W., Cowley, M. J., Hood, C. L., et al. (2012). Differential Regulation of the Let-7 Family of microRNAs in CD4+ T Cells Alters IL-10 Expression. *J. Immunol.* 188 (12), 6238–6246. doi:10.4049/jimmunol.1101196
- Thierry, S., Benleulmi, M. S., Sinzelle, L., Thierry, E., Calmels, C., Chaignepain, S., et al. (2015). Dual and Opposite Effects of hRAD51 Chemical Modulation on HIV-1 Integration. *Chem. Biol.* 22 (6), 712–723. doi:10.1016/j.chembiol.2015.04.020
- Thum, T., Gross, C., Fiedler, J., Fischer, T., Kissler, S., Bussen, M., et al. (2008). MicroRNA-21 Contributes to Myocardial Disease by Stimulating MAP Kinase Signalling in Fibroblasts. *Nature* 456 (7224), 980–984. doi:10.1038/nature07511
- Tian, H., and He, Z. (2018). miR-215 Enhances HCV Replication by Targeting TRIM22 and Inactivating NF-Kb Signaling. *Yonsei Med. J.* 59 (4), 511–518. doi:10.3349/ymj.2018.59.4.511
- Treiber, T., Treiber, N., and Meister, G. (2019). Regulation of microRNA Biogenesis and its Crosstalk with Other Cellular Pathways. *Nat. Rev. Mol. Cell Biol* 20 (1), 5–20. doi:10.1038/s41580-018-0059-1
- Triboulet, R., Mari, B., Lin, Y.-L., Chable-Bessia, C., Bennasser, Y., Lebrigand, K., et al. (2007). Suppression of microRNA-Silencing Pathway by HIV-1 during Virus Replication. *Science* 315 (5818), 1579–1582. doi:10.1126/science.1136319
- Trobaugh, D. W., and Klimstra, W. B. (2017). MicroRNA Regulation of RNA Virus Replication and Pathogenesis. *Trends Molecular Medicine* 23 (1), 80–93. doi:10.1016/j.molmed.2016.11.003
- Tyagi, M., and Kashanchi, F. (2012). New and Novel Intrinsic Host Repressive Factors against HIV-1: PAF1 Complex, HERC5 and Others. *Retrovirology* 9, 19. doi:10.1186/1742-4690-9-19
- van Gent, M., Sparrer, K. M. J., and Gack, M. U. (2018). TRIM Proteins and Their Roles in Antiviral Host Defenses. *Annu. Rev. Virol.* 5, 385–405. doi:10.1146/annurev-virology-092917-043323
- Wang, W.-X., Rajeev, B. W., Stromberg, A. J., Ren, N., Tang, G., Huang, Q., et al. (2008). The Expression of MicroRNA miR-107 Decreases Early in Alzheimer's Disease and May Accelerate Disease Progression through Regulation of -Site Amyloid Precursor Protein-Cleaving Enzyme 1. *J. Neurosci.* 28 (5), 1213–1223. doi:10.1523/jneurosci.5065-07.2008
- Wang, X., Ye, L., Hou, W., Zhou, Y., Wang, Y.-J., Metzger, D. S., et al. (2009). Cellular microRNA Expression Correlates with Susceptibility of Monocytes/macrophages to HIV-1 Infection. *Blood* 113 (3), 671–674. doi:10.1182/blood-2008-09-175000
- Wong, S. T., Zhang, X. Q., Zhuang, J. T., Chan, H. L., Li, C. H., and Leung, G. K. (2012). MicroRNA-21 Inhibition Enhances *In Vitro* Chemosensitivity of Temozolomide-Resistant Glioblastoma Cells. *Anticancer Res.* 32 (7), 2835–2841.
- Wortman, M. J., Krachmarov, C. P., Kim, J. H., Gordon, R. G., Chepenik, L. G., Brady, J. N., et al. (2000). Interaction of HIV-1 Tat with Pur $\alpha$  in Nuclei of Human Glial Cells: Characterization of RNA-Mediated Protein-Protein Binding. *J. Cel. Biochem.* 77 (1), 65–74. doi:10.1002/(sici)1097-4644(20000401)77:1<65:aid-jcb7>3.0.co;2-u
- Wu, M., Fan, B., Guo, Q., Li, Y., Chen, R., Lv, N., et al. (2018). Knockdown of SETDB1 Inhibits Breast Cancer Progression by miR-381-3p-Related Regulation. *Biol. Res.* 51 (1), 39. doi:10.1186/s40659-018-0189-0
- Wu, S., He, L., Li, Y., Wang, T., Feng, L., Jiang, L., et al. (2013). miR-146a Facilitates Replication of Dengue Virus by Dampening Interferon Induction by Targeting TRAF6. *J. Infect.* 67 (4), 329–341. doi:10.1016/j.jinf.2013.05.003
- Wu, X., Zhang, L.-L., Yin, L.-B., Fu, Y.-J., Jiang, Y.-J., Ding, H.-B., et al. (2017). Deregulated MicroRNA-21 Expression in Monocytes from HIV-Infected Patients Contributes to Elevated IP-10 Secretion in HIV Infection. *Front. Immunol.* 8, 1122. doi:10.3389/fimmu.2017.01122
- Yamanaka, S., Oлару, A. V., An, F., Luvsanjav, D., Jin, Z., Agarwal, R., et al. (2012). MicroRNA-21 Inhibits Serpin1, a Gene with Novel Tumour Suppressive Effects in Gastric Cancer. *Dig. Liver Dis.* 44 (7), 589–596. doi:10.1016/j.dld.2012.02.016
- Yang, F., Xu, Z., Duan, S., and Luo, M. (2016). MicroRNA-541 Promotes the Proliferation of Vascular Smooth Muscle Cells by Targeting IRF7. *Am. J. Transl Res.* 8 (2), 506–515.
- Yin, Y., Zhong, J., Li, S.-W., Li, J.-Z., Zhou, M., Chen, Y., et al. (2016). TRIM11, a Direct Target of miR-24-3p, Promotes Cell Proliferation and Inhibits Apoptosis in colon Cancer. *Oncotarget* 7 (52), 86755–86765. doi:10.18632/oncotarget.13550
- Yuan, T., Yao, W., Tokunaga, K., Yang, R., and Sun, B. (2016). An HIV-1 Capsid Binding Protein TRIM11 Accelerates Viral Uncoating. *Retrovirology* 13 (1), 72. doi:10.1186/s12977-016-0306-5
- Zhang, H.-S., Chen, X.-Y., Wu, T.-C., Sang, W.-W., and Ruan, Z. (2012). MiR-34a Is Involved in Tat-Induced HIV-1 Long Terminal Repeat (LTR) Transactivation through the SIRT1/NFkB Pathway. *FEBS Lett.* 586 (23), 4203–4207. doi:10.1016/j.febslet.2012.10.023
- Zhang, H.-S., Wu, T.-C., Sang, W.-W., and Ruan, Z. (2012). MiR-217 Is Involved in Tat-Induced HIV-1 Long Terminal Repeat (LTR) Transactivation by Down-Regulation of SIRT1. *Biochim. Biophys. Acta.* 1823 (5), 1017–1023. doi:10.1016/j.bbamcr.2012.02.014
- Zhang, M. M., Bahal, R., Rasmussen, T. P., Manautou, J. E., and Zhong, X.-b. (2021). The Growth of siRNA-Based Therapeutics: Updated Clinical Studies. *Biochem. Pharmacol.* 189, 114432. doi:10.1016/j.bcp.2021.114432
- Zhang, Q., He, Y., Nie, M., and Cai, W. (2017). Roles of miR-138 and ISG15 in Oral Squamous Cell Carcinoma. *Exp. Ther. Med.* 14 (3), 2329–2334. doi:10.3892/etm.2017.4720
- Zhang, Y., Fan, M., Geng, G., Liu, B., Huang, Z., Luo, H., et al. (2014). A Novel HIV-1-Encoded microRNA Enhances its Viral Replication by Targeting the TATA Box Region. *Retrovirology* 11 (1), 23–15. doi:10.1186/1742-4690-11-23
- Zhang, Z., Wu, Y., Chen, J., Hu, F., Chen, X., and Xu, W. (2021). Expression of microRNA-155 in Circulating T Cells is an Indicator of Immune Activation Levels in HIV-1 Infected Patients. *HIV Res. Clin. Pract.* 22 (3), 71–77.
- Zhao, C., Sun, X., and Li, L. (2019). Biogenesis and Function of Extracellular miRNAs. *ExRNA* 1 (1), 1–9. doi:10.1186/s41544-019-0039-4
- Zhao, J.-J., Lin, J., Lwin, T., Yang, H., Guo, J., Kong, W., et al. (2010). microRNA Expression Profile and Identification of miR-29 as a Prognostic Marker and Pathogenetic Factor by Targeting CDK6 in Mantle Cell Lymphoma. *J. Am. Soc. Hematol.* 115 (13), 2630–2639. doi:10.1182/blood-2009-09-243147

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Chinniah, Adimulam, Nandlal, Arumugam and Ramsuran. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.