# The Involvement of MicroRNAs in SARS-CoV-2 Infection Comorbid with HIV-Associated Preeclampsia

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## Abstract

**Purpose of Review** This review investigated the potential role of microRNAs (miRNAs) in the synergy of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, preeclampsia (PE), and human immunodeficiency virus (HIV) infection. Maternal health is a great concern when treating pregnant women fighting this triad of diseases, which is highly prevalent in South Africa. MicroRNAs are involved in fine-tuning of physiological processes. Disruptions to the balance of this minute protein can lead to various physiological changes that are sometimes pathological.
**Recent Findings** MicroRNAs have recently been implicated in PE and have been linked to the anti-angiogenic imbalance evident in PE. Recent in silico studies have identified potential host miRNAs with anti-viral properties against SARS-CoV-2 infection. Studies have demonstrated dysregulated expression of several miRNAs in HIV-1 infection along with the ability of HIV-1 to downregulate anti-viral host microRNAs.
**Summary** This review has highlighted the significant gap in literature on the potential of miRNAs in women with HIV-associated PE in synergy with the novel SARS-CoV-2 infection. In addition, this review has provided evidence of the critical role that the epigenetic regulatory mechanism of miRNA plays in viral infections and PE, thereby providing a foundation for further research investigating the potential of therapeutic miRNA development with fewer side-effects for pregnant women.

**Keywords** Human immunodeficiency virus · Hypertension · MicroRNA · Preeclampsia · Pregnancy · SARS-CoV-2 infection

## Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late November 2019 and has led to the coronavirus disease 2019 (COVID-19) pandemic [1•]. It

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is believed that SARS-CoV-2 originated from a wild meat market in Wuhan, Hubei, China [2]. Severe acute respiratory syndrome coronavirus 2 transmission occurs across humans regardless of age and sex; however, it is more prevalent amongst the elderly, the overweight, and those with asthma, diabetes, and other immunocompromised conditions [3]. According to the World Health Organization (WHO), South Africa (SA) has the highest COVID-19 prevalence in Africa. Despite an "early hard lockdown" by the country, more than 700,000 South Africans have been infected with SARS-CoV-2 as of October 2020 [4]. Considered to be a low- and middle-income country (LMIC), it seems unlikely that SA will avoid a fall in the local economy. Hence, it is of utmost importance to rapidly discover solutions to overcome the COVID-19 pandemic.

MicroRNAs (miRNAs) are endogenous small non-coding RNAs that are able to post-transcriptionally regulate the expression of proteins through modulation of the protein's messenger RNA. MicroRNAs are approximately 22 nucleotides long and possess a long half-life and stability that is 10 times stronger than mRNAs, even in extracellular fluids like urine and plasma [5]. MicroRNAs are able to degrade mRNA and

suppress protein translation when the 5′ terminal of miRNA pairs with the 3′-untranslated region (3′-UTR) of mRNA [6, 7]. When miRNAs are incompletely complementary to multiple sites in the 3′-UTR, protein synthesis is inhibited [8]. In comparison, when completely base-paired, a single phosphodiester bond is cleaved leading to degradation of the target mRNA [8].

Host miRNAs have been reported to be involved in cell proliferation, angiogenesis, immune cell development, and apoptosis [9]. Differential expression of miRNAs has been implicated in several viral diseases [10], cancer [9], diabetes [11], schizophrenia [12], and cardiovascular diseases [13]. The diverse role of miRNAs ignites the curiosity of its role in contemporary diseases and associated conditions.

Hypertensive disorders in pregnancy (HDP) are one of the commonest direct causes of mortality and morbidity worldwide; approximately 94% of maternal deaths occur in LMIC [14, 15]. Furthermore, it is responsible for 18% of all maternal deaths in SA [14].

Preeclampsia (PE) is an HDP of unknown origin that complicates 5–8% of pregnancies worldwide [16] and occurs more frequently in LMIC compared to high-income countries [15, 17]. Preeclampsia is characterized by new-onset hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) with or without excessive proteinuria (≥300 mg every 24 h); the disorder presents with the clinical signs of hypertension at or after 20-week gestation [18]. The diagnosis of PE is also made in the absence of proteinuria when there is evidence of multi-organ involvement such as acute kidney injury, neurologic signs, liver disease, and intrauterine foetal growth restriction. In addition, evidence of haemolysis, elevated liver enzymes, and low platelet counts leads to a diagnosis of HELLP syndrome [19, 20].

The human immunodeficiency virus (HIV) attack cells of the immune system thereby weakening immunity which leads to the host being susceptible to other infections and diseases. [21]. HIV infection is a global concern with over 30 million people living with HIV at the end of 2019 [22]. In 2019, 13.5% of the South African population was infected with HIV (7.97 million) [23]. South Africa has the highest antiretroviral (ARV) "rollout program" in the world with 4.7 million citizens receiving treatment [24]. The world health organization (WHO) has recommended that all infected humans initiate and continue the life-long use of highly active antiretroviral therapy (HAART) as a treatment for HIV [25]. Pregnant and breast-feeding women are also encouraged to continue with HAART treatment as it was shown to markedly reduce mother to child transmission [25]. However, ARVs may be associated with PE predisposition [26••]. Maternal deaths from HIV infection is high (>34%) in SA followed by obstetric haemorrhage and HDP [15]. Several studies have postulated that HIV infection influences the rate of PE development [27–31].

In light of the high maternal mortality emanating from HIV infection and PE, it is of paramount importance that one examines their interaction with the new deadly COVID-19 pandemic. This review will address the missing gaps in literature concerning the effects of microRNAs in HIV-associated PE comorbid with COVID-19; thereby providing a foundation for further research investigating the triad of inflammatory-related conditions.

## Severe Acute Respiratory Syndrome Coronavirus 2

Severe acute respiratory syndrome coronavirus 2 belongs to the subfamily of Beta coronaviruses, similar to SARS-CoV-1 and MERS-CoV [32]. SARS-CoV-2 is an enveloped virus with positive-sense single-stranded RNA (+ssRNA). Beta coronavirus have been attributed to be the most fatal subfamilies of coronaviruses [32]. Based on current literature, SARS-CoV-2 is composed of four structural and functional proteins which include the spike, membrane, envelope, and nucleocapsid proteins, together with RNA viral genome [33].

The route of COVID-19 spread is similar to other coronaviruses via human-to-human contact. Humans have a basic biological imperative to connect with other people, making human-to-human contact a very efficient way to amplify viral dissemination. However, it is also spread through the oral-faecal route [34, 35]. SARS-CoV-2 infection occurs in three stages [36]. Stage one includes the incubation period which lasts for approximately 5 days. The virus becomes detectable in stage two and the patient displays mild flu-like symptoms. Stage three presents with severe symptoms which include acute respiratory distress syndrome (ARDS), multi-organ involvement, and subsequent death [36].

Upon entry of the virus into the host, SARS-CoV-2 attaches to angiotensin-converting enzyme 2 (ACE 2) receptors of pneumocytes, thereby infecting host cells [37]. Current literature suggests that the receptor-binding domain of SARS-CoV-2 spike protein is activated via cleavage by transmembrane serine protease 2 (TMPRSS2) [38, 39]. SARS-CoV-2 is then able to follow normal trends in viral infection such as replication, maturation, and release of virions. Since ACE 2 receptors are involved in pregnancy [40], it is plausible that SARS-CoV-2 infection predispose pregnancy complications.

## Soluble Angiotensin-Converting Enzyme 2 in SARS-CoV-2 Infection

ACE 2 is a membrane-bound protein (surface protein) that is used by SARS-CoV-2. A Disintegrin and metalloproteinase domain-containing protein 10 (ADAM 10) and ADAM 17 are ectodomain sheddases that are able to cleave the extracellular

domain of ACE 2 between amino acids 716 and 741; producing the soluble form of ACE 2 (sACE 2) that is released into maternal circulation [41].

Individuals with metabolic conditions have a higher expression of angiotensin II, whereas healthy individuals express angiotensin (1-7) [42]. SARS-CoV-2 has a greater affinity for sACE 2 in comparison to the membrane-bound form, indicative of potential therapeutic properties [43]. Soluble ACE 2 can potentially neutralize SARS-CoV-2, thereby reducing viral pathogenicity [42, 43]. In light of the dire pandemic, it is vital that we investigate the properties of sACE 2 and its potential therapeutic benefits in HIV-positive preeclamptic women comorbid with COVID-19.

## The Role of Angiotensin-Converting Enzyme 2 in Pregnancy and Preeclampsia

In a normal physiological environment, the juxtaglomerular cells of the kidney secrete renin, which enzymatically converts angiotensinogen to angiotensin I [44]. Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II [45]. Angiotensin II functions to increase blood pressure by acting on the kidney, brain, arterioles, and adrenal cortex, via its receptors—angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R), shown in Fig. 1 [46]. Angiotensin-converting enzyme 2 serves as a regulatory mechanism by degrading angiotensin II to angiotensin-(1-7) and angiotensin I to angiotensin-(1-9), which have opposing

effects to that of angiotensin II [47]. Thus, ACE 2 maintains a balance in the renin-angiotensin system (RAS).

Pregnancies begin along various psychological, physical, and physiological changes in the body. It is critical that salt-balance and blood pressure (BP) are maintained during pregnancy, which is a principle function of the RAS. From week 6 of gestation, all components of the classical RAS are found in placental tissue, with the potential to regulate villous and extravillous cytotrophoblast (EVT) proliferation, extravillous cytotrophoblast migration, invasion, and placental angiogenesis [48]. Placental RAS is a vital component for the suboptimal regulation of blood flow at the maternal-foetal interface; hence, its dysregulation may predispose HDP such as PE [49, 50]. ACE 2 is expressed in human placenta within syncytiotrophoblasts (ST), cytotrophoblasts (CT), endothelium, and vascular smooth muscle of conducting villi [51]. Interestingly, ACE 2 is also expressed in the invasive interstitial and intravascular trophoblast cell populations, as well as within decidual cells [51]. This highlights the potential for COVID-19 to induce, mimic, or accelerate PE as the SARS-CoV-2 infection exploits ACE 2.

In normal pregnancies, there is a slight increase in the expression of angiotensin II albeit without vasoconstriction or rise in systemic BP because of the development of a refractoriness to the effect of angiotensin II [52, 53]. In contrast, pregnancies complicated by PE are highly sensitized to angiotensin II [54]. This correlates with the clinical findings of PE, which include evidence of elevated BP. Studies by Merrill et al. and Valdés et al. provide evidence of angiotensin 1-7 downregulated in the plasma of PE compared to normotensive
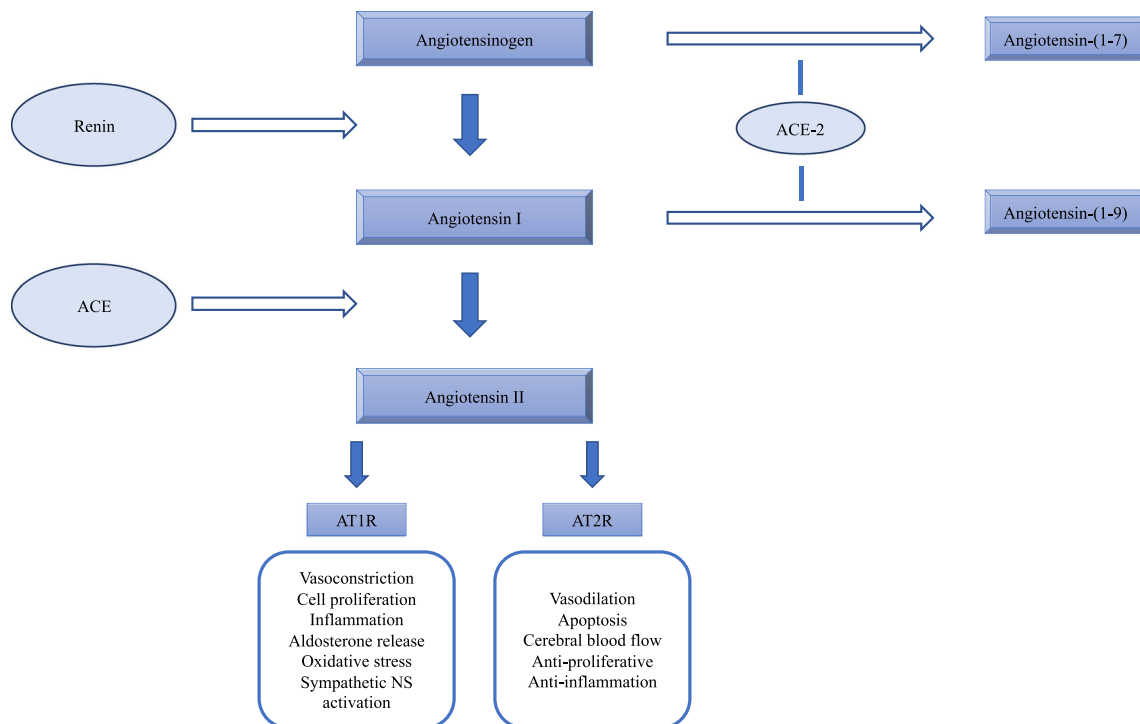


**Fig. 1** Schematic representation of the renin-angiotensin system and the physiological role of ACE-2 receptors

healthy pregnancies [55, 56]. These studies confirm potential of ACE 2 suppression in PE.

## Pathophysiology of Preeclampsia

The etiology of PE has not been fully elucidated; however, it is believed to occur in two stages [57]. The preclinical stage of PE development involves deficient EVT invasion of the uterine spiral arterioles. In this stage, endovascular trophoblast invasion does not progress beyond the decidual segment of the spiral artery; additionally, there is reduced interstitial myometrial invasion [58]. Defective spiral artery remodeling causes placental hypoxia, leading to a shift in the balance of antiangiogenic and proangiogenic factors [58]. Soluble endoglin (sEng) is an antiangiogenic factor that was found to be overexpressed in the serum of preeclamptic women [59]. Endoglin (Eng), a transmembrane glycoprotein that is highly expressed on vascular endothelium, functions as a co-receptor for transforming growth factor beta (TGF-β) [60]. In contrast, sEng inhibits the normal physiology of TGF-β by binding to circulating TGF-β, which leads to dysregulation of TGF-β signalling in ECs [59]. Transforming growth factor receptor I (TGFR-I), otherwise referred to as activin receptor–like kinase 5 (ALK5), and transforming growth factor receptor II (TGFR-II) function as native receptors of TGF-β [61]. It was reported that sEng can potentially inhibit the downstream signalling of TGF-β, including effects on activation of endothelial nitric oxide synthase (eNOS) and vasodilation [59].

Angiogenic imbalance leads to the clinical stage in which an increase in antiangiogenic factors causes widespread damage to the maternal endothelium [62]. This stage presents the clinical features of PE, including hypertension, proteinuria, and intrauterine growth restriction (IUGR) [63]. Delivery of the placenta usually causes rapid resolution of the clinical signs of the disease, making it the only treatment available, which often includes premature delivery of the fetus [64].

## The Expression of microRNAs in Pregnancy

Pregnancy is a time of significant changes in the body in order to prepare for and accommodate the developing fetus. MicroRNAs are able to regulate many of these changes through its control over the expression of mRNA. MicroRNAs have been implicated in the earliest stages of pregnancy, including embryo implantation [65]. After implantation, the trophoblast cell lineage is the first to begin differentiating [66]. Cuman et al. noted miR-661 and miR-372 upregulation in blastocysts that failed to implant [67]; the expression of miR-372 was supported by Rosenbluth et al. as they found a similar expression [68]. In contrast, miR-142-3p is

highly expressed in blastocysts successfully implanted according to a pilot study conducted by Borges et al. [69]. This suggests an involvement of miRNA in ectopic pregnancies and miscarriages. Although differential expression profiling of miRNAs is achievable, the results are not easily reproducible, as evident in significant variations between similar investigations. The difficulty in reproducing results may be explained due to differences in laboratory conduct of the study, methodological differences, and differences in miRNA array panels, as well as the use of either stored or fresh samples [65]. MicroRNA expression is a very dynamic process and varies greatly with the requirements needed at different times [65].

The endometrium is essential for successful embryo implantation. Kresowik et al. identified miR-31 to be overexpressed in endometrium in the mid-secretory phase [70]. MicroRNA-31 is a potent miRNA that inversely regulates forkhead box P3 (FOXP3), a transcription factor for T regulatory cells, and CXCL12, a homeostatic chemokine. CXCL12 is a chemoattractant for uterine natural killer (NK) cells, with the potential to be involved in providing a suitable environment that is immune-tolerant in the secretory phase [65]. Tochigi et al. and Estella et al. investigated the miRNA expression profiles between decidualized human endometrial stem cells (hESC) and control hESC; only miR-155 was commonly expressed in both studies [71, 72].

The attachment of the blastocyst to the uterine endothelial wall occurs 4–6 days post-conception; following this, the placenta begins to develop [73]. MicroRNAs are highly expressed in the human placenta which undergoes physiological changes throughout pregnancy [74, 75]. The precise role of miRNAs in the placenta is yet to be identified. However, the placenta releases placental miRNAs into the maternal circulation, hence is found in maternal serum and plasma and placental tissue. The expression of placental miRNAs is associated with HDPs, such as PE [76]. Previous studies have highlighted the presence of hypoxic conditions in PE compared to healthy controls [58, 77, 78]. MicroRNA-210 is upregulated in trophoblast cells cultured in hypoxic environments, and importantly, in PE [79]. Additionally, miRNAs that are involved in angiogenesis and immune cell development are dysregulated in trophoblastic cells cultured in hypoxic conditions [80–83]. Thus, there exists a possible influence of miRNAs in the progression of normal pregnancies, and in pathological pregnancies.

## MicroRNAs in Pregnancies Complicated by Preeclampsia

There are significant gaps in the investigation of miRNAs in pregnancy-related complications and there is a paucity of data on the miRNA regulation of sEng. Importantly, the miRNA

regulation of sFlt-1 is yet to be elucidated as no miRNA has been directly correlated with the regulation of sFlt-1 [84]. Nevertheless, KG Shyu (2017) reported that miR-208a is responsible for the activation of Eng and collagen I in the stimulation of myocardial fibrosis [85]. This was supported by similar studies [86, 87]. Furthermore, several miRNAs have been suggested to play a role in trophoblast proliferation and invasion, including direct effect on TGF-β signalling. An investigation analyzing the HTR-8/SVneoplacental cell line concluded that miR-376c inhibits ALK5 [88]. Also, miR-29b directly binds to the 3′-UTRs of myeloid cell leukaemia sequence 1, matrix metalloproteinase 2, VEGF-A, and integrin-β1 [89]. When miR-29b is upregulated in the placenta, it causes trophoblastic apoptosis and inhibition of trophoblast invasion and angiogenesis [89]. MicroRNA-193b is increased in preeclamptic patients [90]. Zhou et al. showed that miR-193b-3p decreases migration and invasion of HTR-8/SVneoplacental cells [90]. Interestingly, inhibition of miR-126 in mouse embryos led to abnormal vasculogenesis, haemorrhage, and loss of vascular integrity [91]. This indicated that miR-126 is necessary for proper vessel formation.

## Placental Hypoxia

Abnormal trophoblast invasion of the placenta in PE leads to hypoperfusion of the placenta and ultimately accelerates the placenta into a hypoxic state. The hypoxic state that is associated with PE correlates with the decrease of eNOS and nitric oxide (NO) in preeclamptic patients. MicroRNA-222 was reported to induce the production of eNOS [92] yet was found to be downregulated in the placenta of PE patients [93]. Furthermore, miR-155 was identified to negatively regulate the expression of eNOS in trophoblastic cells [94]. It was also found to be increased in PE placenta, suggesting a negative regulatory role of miR-155 in the migratory behaviour of trophoblasts through the regulation of eNOS [94]. Sun et al. showed that miR-155 exerts its inhibitory effects on eNOS by binding to the 3′-UTR of eNOS mRNA and suggested that silencing of this miRNA can lead to improvement of endothelial dysfunction [95]. Dai et al. reported that miR-155 may inhibit trophoblast invasion and proliferation by downregulating cyclin D1; furthermore, another investigative group reported that miR-155 can inhibit trophoblast invasion by decreasing eNOS expression [96]. This can lead to an exaggerated hypoxic state of the placenta in PE.

Many studies have highlighted the overexpression of miR-210 in preeclamptic placentae and plasma [97•]. MicroRNA-210, believed to be a miRNA that is induced by hypoxia, is one of the most studied miRNAs [98]. The hypoxic state of the placenta in PE causes oxidative stress which leads to the upregulation of hypoxia inducing factor 1-α (HIF-1-α) in placental tissue [98]. Research has revealed that miR-210 is

regulated by HIF-1-α, thereby creating a positive feedback loop inducing hypoxia.

## Angiogenesis

There is evidence of abnormal angiogenesis in PE. Vascular endothelial growth factor (VEGF) is a potent proangiogenic factor that plays a pivotal role in angiogenesis, particularly in endothelial cell proliferation, invasion, and migration [99]. It promotes the production of NO and prostacyclin in the maternal vascular system [100]. Phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2) and sprout-related drosophilia enabled/vasodilator-stimulated phosphoprotein homology 1 (EVH1) domain are a part of the VEGF signalling pathway and are targets of miR-126 [91, 101]. It was reported that miR-126 was downregulated in PE patients and the expression of miR-126 is directly proportional to the expression of VEGF mRNA [101]. VEGF is also targeted by miR-29b, miR-16, and miR-155 as they inhibit the expression of VEGF-A [89, 102, 103]. They also inhibit trophoblast cell invasion and tube formation apart from suppressing VEGF-A; thus, they are involved in placental angiogenesis. Ephrin-B2 (EFNB2) has been identified to influence angiogenesis. MicroRNA-126, miR-20a, miR-17, and miR-20b have been identified as miRNA regulators of EFNB2 and interestingly, they were shown to be differentially expressed in PE [101, 104]. These miRNAs can indirectly regulate the expression of VEGF through the inactivation of EFNB2. The microRNAs greatly involved in PE are summarized in Table 1.

Placental miRNAs are also released into the maternal circulation, contributing the maternal stage of PE; interestingly, miRNAs have also been found to be contained within exosomes, nanoparticle carrier proteins, in the maternal circulation [105]. The release of antiangiogenic factors and other inflammatory mediators into the maternal circulation leads to the systemic endothelial cell inflammation and endothelial cell dysfunction that are characteristic of PE.

## The Role of MicroRNAs in Modulating HIV-1 Infection

HIV infection is one of the more prevalent viral infections in SA [23]. Currently, HIV-infected individuals are treated with HAART [25]. Although HAART is the most effective treatment at present, it is associated with various side-effects. All pregnant women who are HIV-positive are required to adopt the HAART treatment in SA, as it reduces mother-to-child transmission [25]. However, studies have shown that HAART could exhibit a negative influence during pregnancy. Furthermore, there is evidence that the administration of HAART to pregnant HIV-positive patients predisposes the development of PE [106, 107]. In an ideal situation, PE

**Table 1** A summary of microRNAs and their roles in preeclampsia

| MicroRNA | Expression | Target gene | Reference |
|---|---|---|---|
| miR-29b | Upregulated | MCL1, MMP2, VEGF-A, ITGB1 | [89] |
| miR-126 | Downregulated | VEGFA, EFNB2, CRK | [101] |
| miR-222 | Downregulated | eNOS, PTEN, BCL2L11, | [93] |
| miR-155 | Upregulated | eNOS, Cyclin D1 | [94] |
| miR-210 | Upregulated | HIF1-alpha, NF-kBp50 | [97•, 79] |

patients comorbid with HIV infection would have a neutralization of immune response [31, 108]. However, HAART in pregnancy reconstitutes immune response thereby influencing PE development [107, 109, 110]. In light of this, it is essential to thoroughly investigate key regulators in HIV-1 infection in order to identify alternative avenues in the fight against HIV infection globally. Epigenetic regulatory mechanisms, specifically miRNAs, have been shown to play a significant role in HIV infection, as well as other RNA and DNA viral infections [111].

Moreover, miRNAs may be partially responsible for the latency period of the HIV [112]. Huang et al. reported that several miRNAs were differentially expressed in resting CD4$^+$ T cells and activated CD4$^+$ T cells, including miR-28, miR-125b, miR-150, miR-223, and miR-382. These miRNAs have also been shown to target the 3′ ends of HIV-1 mRNAs. Additionally, the group showed that inhibition of these miRNAs can stimulate virus production in resting CD4$^+$ T cells isolated from HIV-positive individuals receiving HAART [10]. It is therefore plausible that these differentially expressed miRNAs can inhibit HIV-1 expression in resting CD4$^+$ T cells, thereby contributing to the viral latency observed in HIV infection.

Apart from direct targeting of the HIV-1 mRNAs by miRNAs, cellular miRNAs can indirectly affect HIV infection through modulating factors that are essential for HIV-1 expression. Cyclin T1 protein is responsible for efficient transcription of the viral genome [113]. A study in 2012 reported that the expression of cyclin T1 is reduced in resting CD4$^+$ T cells; however, it is induced upon activation of CD4$^+$ T cells [114]. A similar investigation identified miR-198 to be downregulated during monocyte to macrophage differentiation and reported that miR-198 is able to suppress HIV-1 replication by downregulating cyclin T1 [115].

Houzet et al. reported that miR-29a and miR-29b are downregulated in HIV-1-infected patients and infected peripheral blood mononuclear cells (PBMCs) [116]. It was reported that the host miRNA, miR-29a targets the *nef* gene of HIV-1. The *nef* protein serves as an accessory protein of HIV and influences viral pathogenesis [117]. The group suggested that expression of miR-29a leads to a reduction of *nef* mRNA and a decrease in viral levels was observed [118]. A study conducted by Nathans et al. observed miR-29a to suppress infectivity

of HIV through direct targeting of HIV-1 transcripts to processing bodies (P bodies) [119]. Chable-Bessia et al. demonstrated that major components of P bodies are able to negatively regulate HIV-1 gene expression via blocking of viral mRNA association with polysomes. They also showed that deletion of these components reactivates the virus in PBMCs isolated from HIV-1 patients receiving HAART [120]. Thus, the downregulation of miR-29a in HIV-infected humans could serve as a mechanism for the maintenance of a latent state of infection. The miR-29 family is composed of miR-29a, miR-29b, and miR-29c. It is important to underline that miR-29a and miR-29b share highly similar sequences [118]. Above and beyond the negative regulation of *nef* expression by miR-29a, Ahluwalia et al. suggested that miR-29a and miR-29b are able to suppress virus replication in HEK293T cells and Jurkat T cells [118]. An in vivo study revealed that a cytokine-microRNA pathway could potentially impact HIV-1 replication. Specifically, the group identified the IL-21/miR-29a pathway to be associated with HIV-1 replication and infectivity [121]. Adoro et al. reported that the IL-21/miR-29a pathway suppresses viral replication since IL-21-stimulated CD4$^+$ T cells upregulate the expression of miR-29a, and IL-21 reverses the downregulation of miR-29a induced by HIV-1 infection [122]. This reiterates the plausibility of the IL-21/miR-29a axis influencing HIV-1 replication and infectivity.

As important as host miRNAs are, viruses bring along with it a set of its own miRNAs, referred to as viral miRNAs (v-miRNAs). The existence of v-miRNAs has been controversial to a degree due to the failure of reproducing findings [123]. The first v-miRNA that was isolated from HIV-1 was discovered in 2004 and was termed miR-N367 [124]. However, subsequent studies that attempted to reproduce the discovery were unsuccessful in their attempts [125–127].

The transactivation-responsive (TAR) element of HIV-1 is an RNA hairpin structure found at the 5′ end of all HIV-1 transcripts [128]. Dominique L Ouellet at al. reported that TAR is a source of miRNAs in cultured HIV-1-infected cell lines and in HIV-1-infected human CD4$^+$ T lymphocytes [128]. TAR has been shown to be involved in cell survival and displays anti-apoptotic properties [129]. HIV-1 TAR miRNAs have been identified to downregulate ERCC1 (excision repair cross complementation group 1) and IER3 (intermediate early response gene 3) which are components

involved in apoptosis and cell survival [130]. Therefore, HIV-1-infected cells may be able to evade death and maintain the virulence of HIV-1.

The novel microRNAs have proven to have highly intricate regulatory roles in the human genomes. However, evidence also supports their existence in both RNA and DNA viruses which can potentially be involved in epigenetic regulation, by both direct and indirect mechanisms. It is thus of paramount importance that miRNAs and v-miRNAs are investigated more thoroughly utilizing newer sequencing technology. The significant impact of miRNAs in viruses and hosts highlights the possibility of their role in other viral infections threatening mankind.

## MicroRNAs in HIV-Associated Preeclampsia and COVID-19

There are numerous reports suggesting an interaction of miRNAs in viral infections. A study investigating the expression of miRNAs in HIV infection found differentially expressed miRNAs between resting CD4^{+} T cells and activated CD4^{+} T cells. Specifically, they found miR-28, miR-125b, miR-150, miR-223, and miR-382 to be differentially expressed [10]. Nersisyan et al. [131] conducted an in silico analysis of potential host miRNAs that can bind coronavirus and identified miR-21, miR-195-5p, miR-16-5p, miR-3065-5p, miR-424-5p, and miR-421 to exhibit this potential.

## MicroRNAs in Angiotensin-Converting Enzyme 2 Receptors

ACE 2 receptors are predominantly found on the endothelial cells [132], heart, blood vessels, and the kidneys [133]. According to several studies, miRNAs are indeed regulators of ACE 2 [134, 135]. ACE 2 abnormalities have been implicated in disorders such as hypertension [136], cardiovascular disease [13], diabetes [11], and old age [13]. MicroRNA-125b is reported to directly target the mRNA of ACE 2 [137]. The same miRNA is found to be downregulated in HIV-infected CD4^{+} T cells and exhibits anti-viral properties [10]. Thus, it is plausible to hypothesize that HIV-positive individuals could be at an increased risk of being infected with SARS-CoV-2 because the host will be experiencing a decline in the expression of miR-125b due to HIV infection. Since miR-125b is a negative regulator of ACE 2 [10], under HIV-positive conditions, the patients will have an increase in the expression of ACE 2, potentially leading to greater viral entry. Supporting this is the work of Batlle et al. who highlighted the fact that healthier people are at a lower risk of developing severe COVID-19 due to lower membrane-bound ACE 2 expression [42]. MicroRNA-125 is also associated with blocking of

apoptosis when downregulated [138]. This possibly allows for the virus to replicate without interruption.

Recently, miR-155 was reported to be associated with ACE 2 modulation by regulating the expression of AT1R by silencing AT1R mRNA [139]. This receptor is involved in cardiovascular homeostasis mechanisms including vasoconstriction, release of catecholamines, and blood pressure evaluation [140]. Vasoconstriction and elevated blood pressure are characteristics that are evident in PE. MicroRNA-155 was observed to be upregulated in the placenta of PE [94] where it negatively regulates the expression of eNOS in trophoblasts. There is a lack of research investigating miR-155 expression in COVID-19. Nevertheless, miR-155 has been described to exhibit anti-viral properties. Silencing of miR-155 led to an approximate 50% increase in the replication of rhinovirus [141]. In a case-control study, miR-155 was found to be upregulated in patients infected with respiratory syncytial virus (RSV), a condition associated with bronchial inflammation [142]. The overexpression of miR-155 shows a correlation with acute inflammatory responses [142]. Theoretically, a preeclamptic patient would be at a greater risk of experiencing severe symptoms of COVID-19, due to the effect of miR-155. Although the miRNA is unlikely to cause a pregnant woman to be at risk of being infected, the endothelial dysfunction seen in PE will be compounded by the dysregulation effects of miR-155 following SARS-CoV-2 infection. Although there is a paucity of data regarding the expression of miR-155 in COVID-19, it is possible to assume an initial downregulation in order to evade immune detection, followed by overexpression when the host develops an inflammatory response to the infection. Research investigating PE patients with SARS-CoV-2 infection will greatly aid in illuminating the effects of miR-155 both in COVID-19 and PE, which can lead to possible therapeutic actions from antagomirs (antagonistic microRNAs).

A geographical study including the USA, Wuhan, Italy, India, and Nepal found several anti-viral host miRNAs that were specific to SARS-CoV-2, one of which was miR-126 [143]. MicroRNA-126 has been identified to target the nucleocapsid of the SARS-CoV-2 [143]. Interestingly, miR-126 is downregulated in PE [101]. The inhibition of miR-126 in mouse embryos was assessed and it was found that it led to abnormal vessel formation and loss of vascular integrity [91]. Since miR-126 is decreased in PE, pregnant women with PE could be at risk of infection due to the loss of an anti-viral miRNA that targets SARS-CoV-2. Furthermore, it is plausible to expect the further downregulation of miR-126 following infection; this can lead to further endothelial cell damage in pregnant women and hence contribute to worsening the effects of PE, possibly inducing death. Additionally, miR-126-3p was found to be downregulated in HIV-1-positive patients receiving HAART. Interestingly, miR-126-3p was upregulated in patients with HAART resistance in comparison to

patients without resistance [144••]. It was indicated that this is suggestive of miR-126 being linked with HIV treatment failure [144••]. This evidence has possible detrimental results for HIV-associated PE women as both conditions exhibit a decrease in miR-126. Hence, patients with HIV-associated PE could be at a greater risk of both contraction of SARS-CoV-2 infection and the experiencing of severe COVID-19. Furthermore, Li et al. found several miRNAs to be differentially expressed in the peripheral blood of patients with COVID-19 [145••]. There is a great need to investigate the expression of miRNAs in COVID-19, which is yet to be achieved.

## Conclusion

Currently, there exists a wide gap in literature interrelating miRNAs and SARS-CoV-2 infection. Analysis of the differential expression of miRNAs in COVID-19 can help identify those at risk as well as aid in the development of therapeutic approaches. An inflammatory response is a common characteristic shared between SARS-CoV-2 infection, pregnancy, PE, and HIV infection. Maternal health should be of utmost importance when SARS-CoV-2 infection arises in HIV-positive preeclamptic women. Thus, further research investigating the functionality of microRNAs on the synergy of SARS-CoV-2 infection, PE, and HIV infection could provide significant breakthroughs that will enhance the treatment in pregnant women. Understanding how miRNAs are affected and identifying which miRNAs are aberrantly expressed will accelerate the development of a vaccine that will also be safe for pregnant women diagnosed with HIV-associated PE.

## Declarations

**Human and Animal Rights and Informed Consent**    This article does not contain any studies with human or animal subjects performed by any of the authors.

**Conflict of Interest**    The authors declare no conflicts of interest relevant to this manuscript.

## References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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