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# Neuropilin-1 in the pathogenesis of preeclampsia, HIV-1, and SARS-CoV-2 infection: A review

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## ABSTRACT

This review explores the role of transmembrane neuropilin-1 (NRP-1) in pregnancy, preeclampsia (PE), human immunodeficiency virus type 1 (HIV-1) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Since these conditions are assessed independently, this review attempts to predict their comorbid clinical manifestations. Dysregulation of NRP-1 contributes to the pathogenesis of PE by (a) impairing vascular endothelial growth factor (VEGF) signaling for adequate spiral artery remodeling and placentation, (b) inducing syncytiotrophoblast (ST) cell apoptosis and increasing ST-derived microparticle circulation and (c) by decreasing regulatory T cell activity predisposing maternal immune intolerance. Although NRP-1 is upregulated in SARS-CoV-2 placentae, its exploitation for SARS-CoV-2 internalization and increased infectivity may alter angiogenesis through the competitive inhibition of VEGF. The anti-inflammatory nature of NRP-1 may aid its upregulation in HIV-1 infection; however, the HIV-accessory protein, tat, reduces NRP-1 expression. Upregulated NRP-1 in macrophages and dendritic cells also demonstrated HIV-1 resistance/reduced infectivity. Notably, HIV-1-infected pregnant women receiving antiretroviral therapy (ART) to prevent vertical transmission may experience immune reconstitution, impaired decidualization, and elevated markers of endothelial injury. Since endothelial dysfunction and altered immune responses are central to PE, HIV-1 infection, ART usage and SARS-CoV-2 infection, it is plausible that an exacerbation of both features may prevail in the synergy of these events. Additionally, this review identifies microRNAs (miRNAs) mediating NRP-1 expression. MiR-320 and miR-141 are overexpressed in PE, while miR-206 and miR-124-3p showed increased expression in PE and HIV-1 infection. Additionally, miR-214 is overexpressed in PE, HIV-1 and SARS-CoV-2 infection, implicating treatment strategies to reduce these miRNAs to upregulate and normalize NRP-1 expression. However, inconsistencies in the data of the role and regulation of miRNAs in PE, HIV-1 and SARS-CoV-2 infections require clarification. This review provides a platform for early diagnosis and potential therapeutic intervention of PE, HIV-1, and SARS-CoV-2 infections independently and as comorbidities.

## 1. Introduction

The burden of maternal mortality attributed to hypertensive disorders of pregnancy (HDP), particularly preeclampsia (PE), in low- and middle-income countries (LMICs), such as South Africa (SA), is high (Lewis, 2008; Girum and Wasie, 2017). Thus, there is an urgent need to

reduce the maternal mortality ratio in SA to attain the global Sustainable Developmental Goals 2016–2030 (World Health Organization, 2015; United Nations, 2016; National Committee for Confidential Enquiry into Maternal Deaths, 2018). Due to the high prevalence of human immunodeficiency virus type 1 (HIV-1), SA has the highest antiretroviral therapy (ART) rollout globally including the use of these drugs for the

**Abbreviations:** Akt, Protein kinase B; ART, Antiretroviral therapy; COVID-19, Coronavirus disease 2019; FGR, Fetal growth restriction; HDP, Hypertensive disorders of pregnancy; HIV-1, Human immunodeficiency virus type 1; LMICs, Low- and middle- income countries; NRP-1, Neuropilin-1; PI3K, Phosphatidylinositol 3-kinase; PlGF, Placental growth factor; PMTCT, Prevention of mother-to-child transmission; PE, Preeclampsia; SARS-CoV-2, Severe acute respiratory coronavirus 2; SEMA, Semaphorin; sFlt-1, Soluble fms-like tyrosine kinase 1; ST, Syncytiotrophoblast; STBM, Syncytiotrophoblast microparticles; tat, Transactivator of transcription protein; Tregs, CD4+ regulatory T cells; VEGF, Vascular endothelial growth factor; VEGFR, VEGF receptor.

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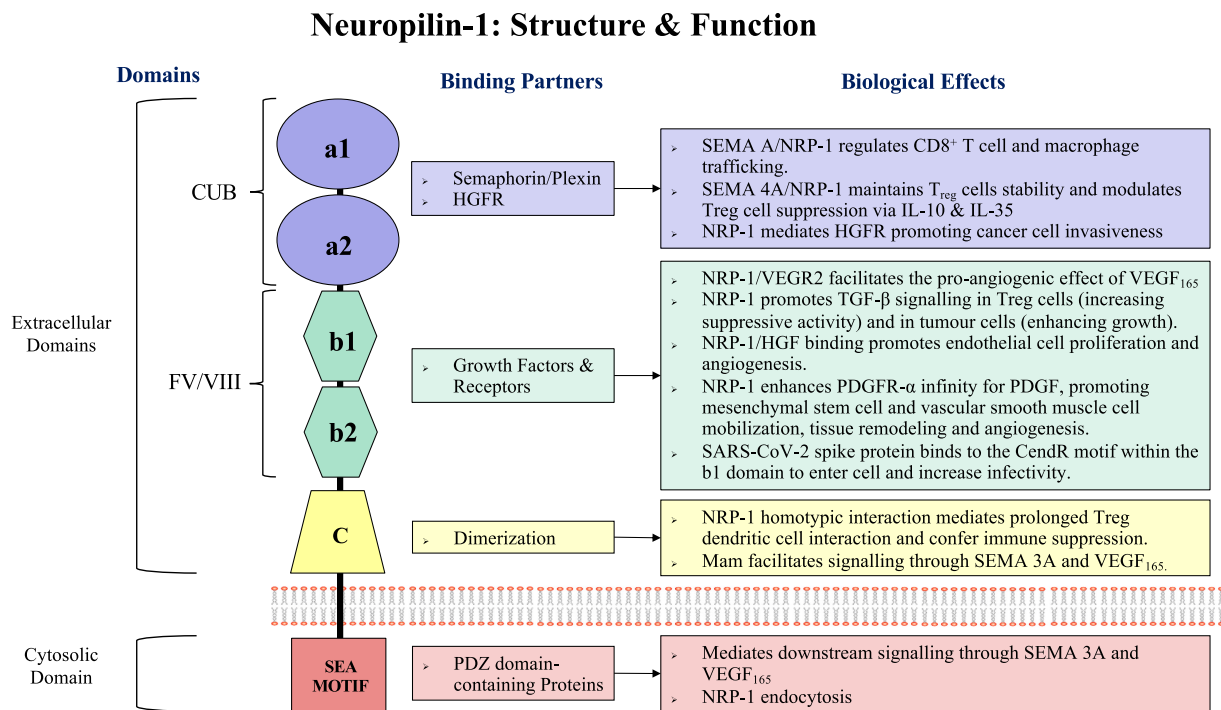
prevention of mother-to-child transmission (PMTCT) (Pattinson, 2014; Woldeesenbet et al., 2018). Increased PE prevalence and mortality rates have been associated with adverse effects of HIV-1 infection and ART usage (Frank et al., 2004; Sebitloane and Moodley, 2017a; Sebitloane and Moodley, 2017b). Moreover, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, causing the coronavirus disease (COVID-19) pandemic, has devastated the South African healthcare system. Since PE and HIV-1 infection increases susceptibility to COVID-19 morbidity and mortality, it is urgent to establish the relationship between PE, HIV-1 infection, ART usage, and COVID-19 (Brown et al., 2021; Naidoo et al., 2021).

The transmembrane neuropilin-1 (NRP-1) protein is a multifunctional signaling protein involved in cell migration and invasion, angiogenesis, tumor progression, SARS-CoV-2 cell entry, axonal guidance, and immune function (Mayi et al., 2021). NRP-1 is also highly expressed in female reproductive tissue, where it plays an integral role in maintaining maternal immune tolerance and placentation (Arad et al., 2017). Previous research highlights defective NRP-1 expression in the pathogenesis of PE and its upregulation in SARS-CoV-2 infections (Ochiumi et al., 2006; Maulik et al., 2016; Xu et al., 2016; Arad et al., 2017; Cantuti-Castelvetri et al., 2020). The influence of NRP-1 in normotensive pregnant and preeclamptic women of African ancestry living with HIV-1 infection and the effects of ART superimposed on COVID-19 remains unknown. In addition, several microRNAs (miRNAs) mediating NRP-1 expression are dysregulated in PE, HIV-1 infection and COVID-19, implicating their role in the pathogenesis of these disorders. Therefore, this review discusses the role and regulation of NRP-1 in PE, HIV-1 infection, and COVID-19, as well as possible interactions/comorbidities and potential therapeutic intervention/management strategies.

## 2. Neuropilin-1: Structure and function

NRP-1 is segmented into several domains, namely, the extracellular complement C1r/C1s, uEGF bone morphogenetic protein 1 (CUB) domain (denoted 'a1/a2'); the coagulation factors V/VIII domain (denoted 'b1/b2'); the homologous meprin protease (MAM), A5 antigen, receptor tyrosine phosphatase  $\mu$  and K domain (denoted 'c'); and the intracellular PSD-95/Dlg/ZO-1 homology (PDZ) domain-binding motif (SEA) (Fig. 1) (Nakamura and Goshima, 2002). The CUB or a1/a2 domain interacts with the semaphorin (SEMA) group of ligands to modulate immune cell trafficking and CD4+ regulatory T cells (Tregs) activity as well as to maintain its stability (Nakamura and Goshima, 2002; Chuckran et al., 2020). The FV/VIII or b1/b2 domain associates with vascular endothelial growth factor (VEGF) groups promoting endothelial cell proliferation, migration, and angiogenesis (Chuckran et al., 2020). The c domain mediates homodimerization or heterodimerization of the receptors for cell adhesion and signal transduction (Nakamura and Goshima, 2002). Lastly, the SEA motif binds to the G Alpha Interacting Protein (GAIP) C-terminus/synectin, mediating intracellular signaling and receptor internalization (Chuckran et al., 2020).

NRP-1 has a high affinity to VEGF165 and placental growth factor (PlGF), particularly type 2 (Felmeden et al., 2003). Amino acids present at the carboxyl-terminal chain of the exon 7-encoded domain of VEGF165 mediate its binding capacity and specificity for NRP-1 (Neufeld et al., 1999; Wu et al., 2010). Although VEGF-A has a weaker affinity for VEGFR-2, it is an essential mediator of angiogenesis in the presence of NRP-1, boosting endothelial cell migration and proliferation (Shibuya, 2006; Pandey et al., 2018). In the presence of VEGF165, NRP-1 binds to VEGF2, which stimulates phosphatidylinositol 3-kinase (PI3K) to activate protein kinase B (Akt), thereby facilitating angiogenesis (Hong et al., 2007). NRP-1 is a dual receptor for VEGF-A and SEMA 3A, although SEMA 3A has anti-angiogenic properties in vitro,



**Fig. 1. Neuropilin-1 structure, ligands, and biological effects.** Adapted from (Chuckran et al., 2020). Abbreviations: C-end rule motif (CendR); CD4+ regulatory T cell (Treg); Coagulation factors, V/VIII domains (b1/b2); Complement C1r/C1s, uEGF bone morphogenetic protein 1 (CUB or a1/a2); Hepatocyte growth factor (HGF); Interleukin-10 and -35 (IL-10 and IL-35); Meprin, A-5 protein, and receptor protein-tyrosine phosphatase mu domain (c); Met/hepatocyte growth factor receptor (HGFR); Neuropilin-1 (NRP-1); Platelet-derived growth factor (PDGF); Platelet-derived growth factor receptor alpha (PDGFR- $\alpha$ ); PSD-95/Dlg/ZO-1 homology domain (PDZ); Semaphorin (SEMA A, 3A and 4A); Serine/Glutamate/Alanine sequence (SEA); Severe acute respiratory coronavirus 2 (SARS-CoV-2); Vascular endothelial growth factor 165 (VEGF165); VEGF receptor 2 (VEGFR-2).

causing endothelial cell adhesion, migration, and survival to be compromised (Romano et al., 2016). It is, therefore, plausible that an imbalance of competitive inhibitors such as VEGF165 and SEMA 3A will affect angiogenesis (Miao and Klagsbrun, 2000). Furthermore, NRP-1 is a crucial component required for initiating the primary immune response (Tordjman et al., 2002; Vadasz et al., 2010). In addition, it facilitates interactions between dendritic and Treg cells, thereby contributing to peripheral tolerance (Sarris et al., 2008; Vadasz et al., 2010). Finally, the pro-angiogenic and immune functions of NRP-1 are also essential for normal successful pregnancy.

### 3. Neuropilin-1 in normal pregnancy

NRP-1 is highly expressed in the human decidua, syncytiotrophoblast (ST) and extravillous trophoblast cells, endothelial cells of placental villous capillaries and vessels, where it plays a fundamental role in establishing and sustaining the maternal-fetal microenvironment (Baston-Buest et al., 2011). Halder et al., reported an upregulation of NRP-1 in the decidual bed of mice (Halder et al., 2000). Baston-Buest et al., demonstrated a strong mRNA and protein expression of NRP-1 in trophoblast cells in vitro and showed that this expression occurred across all three trimesters of pregnancy; the highest expression occurring in the first trimester with a decline to a moderate/low expression in late pregnancy (Baston-Buest et al., 2011). This observation may contribute to the formation of new blood vessels early in pregnancy to facilitate implantation and placentation (Krüssel et al., 2001).

During implantation, alloantigens of paternal origin are expressed by the embryo and contribute to inflammation (Robertson et al., 2018). Human chorionic gonadotropin (hCG) is secreted by the blastocyst immediately after fertilization and has chemoattractant properties that recruit Tregs (Schumacher et al., 2009). The presence and activation of Tregs at the maternal-fetal interface are essential for physiological adaptation that prevents alloantigen-associated inflammation and establishes immune tolerance (Guerin et al., 2009; Moldenhauer et al., 2019). Tregs control effector immunity, suppress inflammation and facilitate maternal vascular adaptations, enabling trophoblast invasion and blood perfusion to the developing fetus (Robertson et al., 2019). Reduced Tregs or a lack of functional competency have been linked to idiopathic infertility and recurrent miscarriage, as well as pregnancy problems such as PE and fetal growth restriction caused by placental insufficiency (Schumacher et al., 2009; Moldenhauer et al., 2019; Robertson et al., 2019).

NRP-1, in addition to its involvement in tumor angiogenesis, exacerbates Treg cell suppression and restriction of long-lasting CD8<sup>+</sup> T cell responses (Chuckran et al., 2020). NRP-1 is highly expressed by Tregs and is required for intrinsic cell stability (Chuckran et al., 2020). In miscarriage and ectopic pregnancies, reduced hCG secretion by the blastocyst hinders Treg cell recruitment and function at the maternal-fetal interface (Schumacher et al., 2009). Furthermore, reduced Treg cell activity is significantly attributed to its decreased expression of NRP-1, forkhead box P3 (Foxp3), interleukin-10 (IL-10), and transforming growth factor-beta (TGF- $\beta$ ) mRNA levels compared to normal pregnancies, thereby implicating NRP-1 in maternal immune tolerance (Schumacher et al., 2009).

NRP-1 is also essential for healthy fetal growth. Dysregulated neuronal and endothelial NRP-1 gene expression in mice predisposes to embryonic death due to complications during cardio-pulmonary development (Kitsukawa et al., 1995; Kitsukawa et al., 1997). Therefore, the tight regulation of NRP-1 expression is essential during pregnancy.

### 4. Preeclampsia

PE is a human pregnancy disorder clinically manifesting with new-onset hypertension after 20 weeks of gestation (Magee et al., 2021). Proteinuria is a common symptom of PE; however, it is not a criterion for diagnosis (Brown et al., 2018; Magee et al., 2021). End-organ

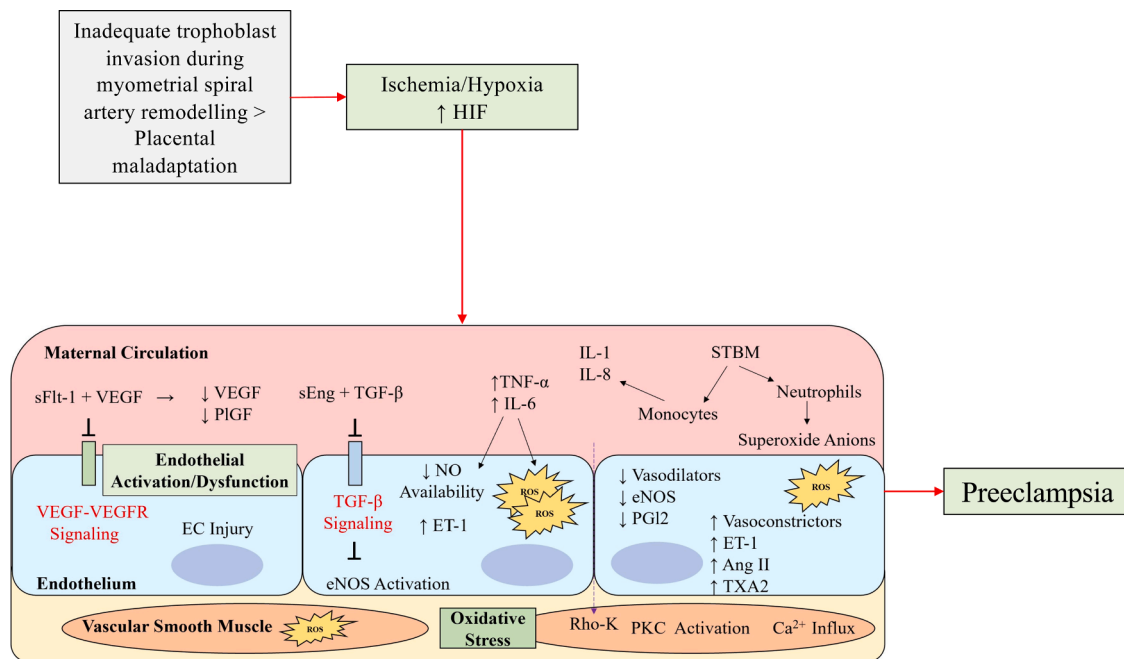
dysfunctions such as acute kidney injury, neurological symptoms, liver dysfunction, the HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets), and/or uteroplacental dysfunction, such as fetal growth restriction (FGR), may also feature in PE (Brown et al., 2018; Magee et al., 2021). Globally, PE complicates 5-7% of pregnancies, often escalating to >10% in LMICs and is annually accountable for a substantial proportion of maternal and fetal mortality (Wanderer et al., 2013; Brown et al., 2018). The pathogenesis of PE involves inadequate extravillous trophoblast invasion with a subsequent lack of myometrial spiral artery remodelling, leading to placental maladaptation (Naicker et al., 2013; Rana et al., 2019). As a result of the hypoxic-ischemic microenvironment, the balance between pro- and anti-angiogenic proteins in maternal circulation is disrupted (Redman and Sargent, 2005; Jardim et al., 2015). These occurrences ultimately predispose pregnant women to the widespread multi-organ endothelial dysfunction observed in PE.

The angiogenic and inflammatory profile of PE plays a crucial role in the onset of maternal endothelial dysfunction (Naidoo et al., 2021). Increased anti-angiogenic factors such as soluble fms-like tyrosine kinase (sFlt-1) antagonize VEGF and PlGF binding to VEGFR-2 on endothelial cells, thereby hindering placentation in PE (Possomato-Vieira and Khalil, 2016). Moreover, elevated soluble endoglin (sEng) impedes TGF- $\beta$  signaling for endothelial nitric oxide synthase (eNOS) bioavailability for vasodilation (Moghaddas Sani et al., 2019). Following deficient trophoblast invasion during spiral artery remodeling, the hypoxic-ischemic milieu of the placenta prompts the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukins (IL-1, IL-6 and IL-8) and syncytiotrophoblast microparticles (STBM) which further deter eNOS and prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) production for effective vasodilation (Moghaddas Sani et al., 2019). This is achieved by leukocyte recruitment and subsequent oxidative/nitrosative stress (Paladugu et al., 2003). Additionally, an incline of agonist autoantibodies against angiotensin receptors (AT1-AA) released from the preeclamptic placenta facilitates angiotensin II (Ang II) receptor sensitivity and increases placental oxidative stress (Brewer et al., 2013; Campbell et al., 2018). These events ultimately lead to increased vasoconstriction predominantly by elevated endothelin-1 (ET-1) circulation, which is then sustained by calcium influx and vascular resistance during endothelial damage in PE, as seen in Fig. 2 (Maynard et al., 2003; Touyz et al., 2018).

### 5. Neuropilin-1 in preeclampsia

NRP-1 expression is reduced in the ST villous layer of PE placentas compared to normotensive pregnancies, indicating its involvement in the development of PE (Arad et al., 2017). Another study revealed that NRP-1 and VEGF were significantly lower in both PE and homocysteine-induced PE in mice, predisposing endothelial damage seen in PE (Xu et al., 2016). Yang et al., showed that increased NRP-1 expression, regulated by RNA-binding protein [quaking I-5 (QKI-5)], significantly enhanced trophoblast proliferation in vitro and in vivo. In addition, these authors showed significantly reduced expressions of QKI-5 and NRP-1 in PE placentae as well as in trophoblasts exposed to hypoxic conditions (Yang et al., 2021). Furthermore, QKI-5 directly interacted with the 3'-UTR region of NRP-1 to mediate cell proliferation and migration via matrix metalloproteinase-9 (Yang et al., 2021). FGR pregnancies complicated with absent end-diastolic flow in the umbilical artery showed reduced placental NRP-1 expression, correlating with PE development (Maulik et al., 2016). NRP-1 is also downregulated in pregnancies following assisted reproductive technologies, a known risk factor of PE development (Omani-Samani et al., 2020).

In addition to the pro-angiogenic implication of reduced NRP-1 in PE, the receptor also regulates apoptosis which is also associated with the pathogenesis of PE (Ochiumi et al., 2006). Shedding of STBM from the placenta into maternal blood occurs in normal pregnancies and is exacerbated during PE due to elevated apoptosis or aponecrosis



**Fig. 2. Maternal endothelial dysfunction in preeclampsia.** Adapted from (Naidoo et al., 2021). Abbreviations: Angiotensin II (Ang II); Endothelial nitric oxide synthase (eNOS); Endothelin-1 (ET-1); Hypoxia-inducible factor (HIF); Interleukin-1, 6, and 8 (IL-1, IL-6, and IL-8); Nitric oxide (NO); Prostaglandin (PGI2); Protein kinase C (PKC); Placental growth factor (PlGF); Reactive oxygen species (ROS); Soluble endoglin (sEng); Soluble fms-like tyrosine kinase-1 (sFlt-1); Syncytiotrophoblast microparticles (STBM); Transforming growth factor-β (TGF-β); Tumor necrosis factor-α (TNF-α); Thromboxane A2 (TXA2); Vascular endothelial growth factor (VEGF); VEGF receptor (VEGFR).

(Huppertz et al., 1998). These microparticles induce systemic inflammation (Naidoo et al., 2021). Arad et al., showed that NRP-1 (anti-apoptotic) immunostaining of the ST cells was highly concentrated within syncytial knots (aged ST cells). This localization of NRP-1 within the syncytial knots differs from previous descriptions of other anti-apoptotic proteins that showed reduced levels in this area (Arad et al., 2017). Notably, the STBM in PE serve as a stimulus for systemic inflammation and endothelial cell injury (Huppertz, 2010; Sharp et al., 2010).

Previous research supports the anti-apoptotic ability of NRP-1, in cancer and rheumatoid arthritis, due to the regulation of B-cell lymphoma-2 (Bcl-2) expression and Bcl-2 associated X protein (Bax) translocation (anti-apoptotic proteins) (Bachelder et al., 2001; Kim et al., 2006; Ochiuni et al., 2006; Riese et al., 2012). Therefore, reduced expression of NRP-1 in preeclamptic placentae may contribute to the apoptotic process (Arad et al., 2017). PE is also associated with elevated apoptosis of extravillous trophoblasts cells (Naicker et al., 2013). MiRNAs have also been implicated in the regulation of Tregs in PE, particularly in the downregulation of MiR-210 and MiR-155, affecting maternal immune tolerance (Chen et al., 2019; Schjenken et al., 2020). Previous studies have identified HIV-1 infection and ART usage for PMTCT as risk factors for PE due to their adverse side effects, which exacerbate the anti-angiogenic and pro-inflammatory milieu of PE (Tooke et al., 2016).

### 6. Neupilin-1 in human immunodeficiency virus infection

In 2020, the number of HIV-1 infections was estimated to be 37.7 million in the global population, of which 25.4 million emanated from the African continent (World Health Organisation, 2021). The 2021 mid-year statistics showed that 8.2 million South Africans are reportedly living with HIV-1 infection, including women of child-bearing age and pregnant women (Stats SA, 2021). Trans-activator of transcription (tat), an HIV-1-1 accessory protein, has been shown to mimic VEGF; however, its involvement in angiogenesis is unclear (Padayachee et al., 2019).

Since ART is a global standard of care to improve the immunological incompetency seen in HIV-1 infection and for PMTCT, 97% of South African pregnant women living with HIV-1 infection receive various forms of ART (World Health Organization, 2010, 2019). ART restores immune function in HIV-1-infected individuals; therefore, pregnant women receiving ART may be at risk for severe comorbidity with PE (French et al., 2000; Tooke et al., 2016). Several studies highlight the impact of ART in decidualization and placentation, prompting maternal endothelial dysfunction and the hypertensive hallmark in PE (Autran et al., 1999; Powis and Shapiro, 2014; Hernández et al., 2017; Song et al., 2018; Naidoo et al., 2021).

An upregulation in VEGFR-2 and its co-receptor NRP-1 occurs in podocytes of HIV-1-1 transgenic mice, possibly attributed to the anti-inflammatory nature of NRP-1 (Korgaonkar et al., 2008). Notably, tat is an HIV-1 regulatory protein that optimizes viral infectivity (Debaixieux et al., 2012). Its arginine and lysine sequence closely resembles that of VEGF (Albini et al., 1996; Zhou et al., 2013). Therefore, tat protein hinders VEGF-induced extracellular-signal-regulated kinase (ERK) activation and mitogenesis in endothelial cells via competitive inhibition of VEGFR and NRP-1 signaling. This downregulates angiogenesis in vitro at concentrations similar to those which inhibit VEGF receptor binding (Jia et al., 2001). A recent novel study identified NRP-1 as an antiviral protein for the treatment of HIV-1 infection (Wang et al., 2022). Wang et al., observed resistance to HIV-1 infection in myeloid cells [macrophages and dendritic cells (DCs)] due to their high expression of transmembrane NRP-1 compared to CD4+ T cells (Wang et al., 2022). Furthermore, this study demonstrated that NRP-1 silencing facilitated the transmission of HIV-1 in macrophages and DCs significantly and amplified virion infectivity in these cells (Wang et al., 2022). However, the lack of literature on NRP-1 in HIV-1 infection prompts future research examining its regulation in viral infection.

### 7. COVID-19: The global pandemic

The coronavirus disease (COVID-19) has claimed more than 6.2

million lives, with approximately 525 million confirmed cases worldwide, as of May 2022 (World Health Organization, 2022). Prior to the COVID-19 vaccine rollout, pregnant women with COVID-19 were more susceptible to adverse outcomes requiring hospitalization and intensive care unit admission than non-pregnant women (Sheffield, 2021). Fifty-five percent of the hospitalized patients were asymptomatic, while one-fifth had underlying medical conditions; moreover, a two percent miscarriage rate was also noted (Sheffield, 2021). At present, over 11.3 billion vaccine doses have been administered globally, which show promising protective properties against severe SARS-CoV-2 infection (World Health Organization, 2022). Observational studies raised no major concerns of adverse effects and short-term obstetric outcomes following vaccinations in pregnant women (Bleicher et al., 2021; Bookstein Peretz et al., 2021; Goldshtein et al., 2022). Moreover, a significant secretion of SARS-CoV-2-specific IgA and IgG was reported in human milk implicating the possibility of passive immunity transfer from vaccinated women to infants through breastfeeding (Valcarce et al., 2021). Similar to the general population, pregnant women showed high vaccine effectiveness during SARS-CoV-2 infection; however, long-term surveillance is still underway (Dagan et al., 2021; Goldshtein et al., 2021).

Endothelial dysfunction and inflammation are central to the systemic manifestations of COVID-19 (Kaur et al., 2020). Following SARS-CoV-2 infection, the lung pathology of moderate/severe cases presented with neutrophilia (Fox et al., 2020). This observation was accompanied by an upregulation of expressions of E-selectin, P-selectin, adhesins, cadherins, as well as dysregulated angiogenic factors (VEGFR-1, VEGFR-2, PECAMs, ICAMs, and VCAM-1) and hypoxia (Kaur et al., 2020). Alterations of these circulating proteins increase vascular permeability in pulmonary and acute capillaries with subsequent expulsion of neutrophils into the alveolar space, compromising the alveolar-capillary barrier (Herold et al., 2013; Kaur et al., 2020). Additionally, the excess circulating neutrophils may promote neutrophil extracellular traps (NETs), which aggregate with platelets and induce coagulation (Sørensen and Borregaard, 2016; Zuo et al., 2020).

Increased chemotaxis prompts the macrophage activation syndrome (MAS) and upregulates pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  (Schulert and Grom, 2015). Moreover, reactive oxygen species generated by neutrophils damage the endothelium and further contribute to the COVID-19 cytokine storm (Soy et al., 2020). The inflammatory cascade promotes endothelial activation and capillary leakage, resulting in circulatory collapse and distress (Jin et al., 2020). Persistent endothelial dysfunction expedites the clotting cascade and microvascular obstruction, leading to multi-organ failure (Kaur et al., 2020).

Notably, the endothelial pathology observed in COVID-19 positive individuals closely resembles the pro-inflammatory state of PE (Naidoo et al., 2021). COVID-19 infected placentas showed hypoxia with a subsequent decline in maternal vascular perfusion, implying the presence of systemic inflammation (Shanes et al., 2020). Furthermore, an incline was observed in the sFlt-1/PlGF ratio in COVID-19 positive patients compared to COVID-19 negative pneumonia and healthy patients (Giardini et al., 2020). Similarly, an increased sFlt-1/PlGF ratio is noted in PE and is currently used in its diagnosis and management (Hernández-Pacheco et al., 2020). Therefore, it is suggestive that COVID-19 increases the risk of PE development and vice versa (Mendoza et al., 2020; Phoswa and Khaliq, 2020).

## 8. Neuropilin-1 in SARS-CoV-2 infection

The angiotensin-converting enzyme 2 (ACE2) receptor, previously identified as an entry receptor for SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), displays a higher affinity for the SARS-CoV-2 receptor-binding domain (RBD) compared to the SARS-CoV RBD (Shang et al., 2020). Similar to SARS-CoV and MERS-CoV, the SARS-CoV-2 spike protein is proteolytically cleaved at the S1/S2 site for

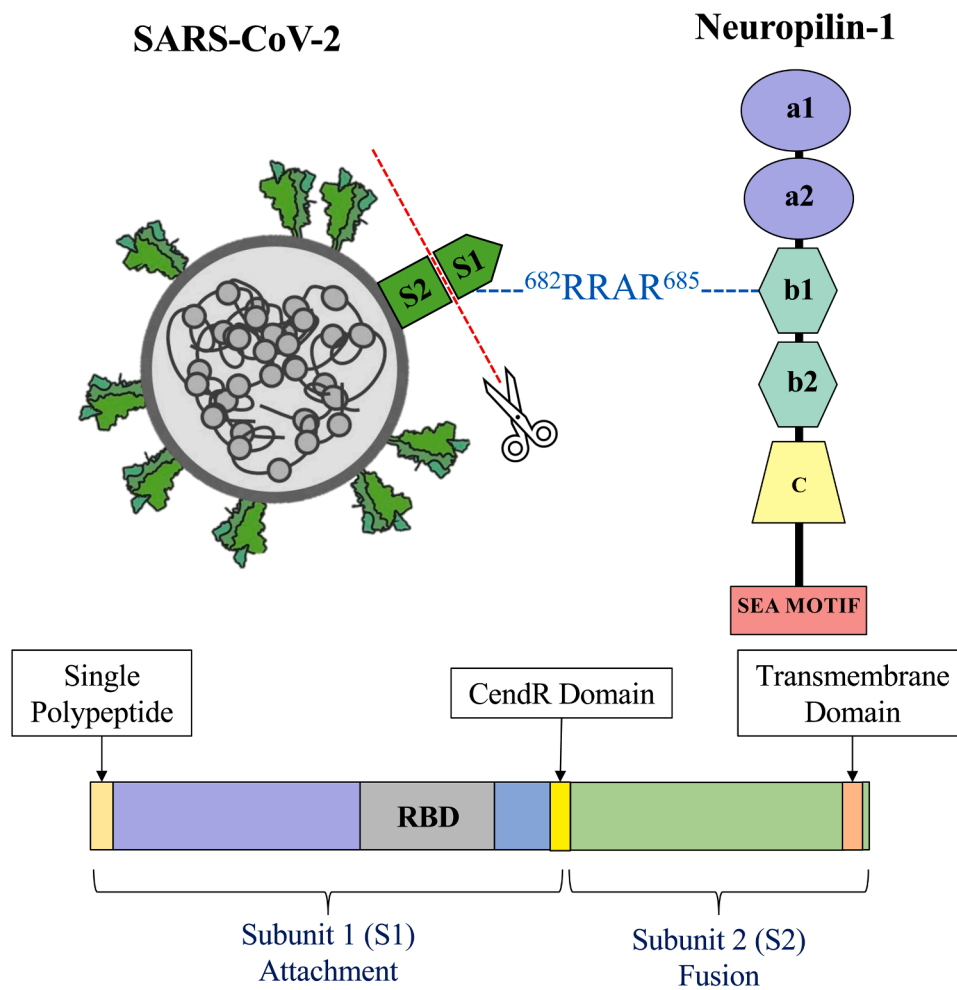
successful infection of the human host cell (Wrobel et al., 2020). Studies highlight several cofactors such as transmembrane serine protease 2 (TMPRSS2), TLR4 (Toll-like receptor 4), furin, endosomal cathepsin B/L (CatB/L), heparan sulfate proteoglycans (HSPGs) and NRP-1 that aid ACE2 receptors by playing an integral role in SARS-CoV-2 spike protein priming and increasing viral infectivity (Evans and Liu, 2021; Zhao et al., 2021).

NRP-1 is directly involved in SARS-CoV-2 internalization and infectivity (Cantuti-Castelvetri et al., 2020). Upon infection, the SARS-CoV-2 spike protein is cleaved by endogenous furin thereby exposing the C-end rule (CendR) motif in S1 (Coutard et al., 2020). Since the CendR binding pocket lies within the b1 domain of NRP-1, the NRP-1 binds to the exposed C-terminal RRAR amino acid motif (res. 682–685) of the S1 subunit, potentiating increased viral endocytic internalization, viral cargo dissemination and infectivity (Fig. 3) (Coutard et al., 2020; Balistreri et al., 2021). The binding of NRP-1 catalyzes viral spike protein complex destabilization thereby activating the detachment of S2 from the S1 subunit. Subsequently, the S2 domain undergoes fusion and replication within the host cell (Gudowska-Sawczuk and Mroczko, 2021). Notably, VEGF165 also binds to the b1 domain of NRP-1, thereby implicating competitive dysregulation of angiogenesis (Pan et al., 2007; Daly et al., 2020). The capsid proteins of several viruses contain CendR motifs which may be exposed following proteolytical cleavage (Teesalu et al., 2009). Similar to SARS-CoV-2 exploitation of NRP-1, other viruses have also shown to manipulate the CendR motif for host cell infection (Table 1).

The dissemination and dysregulation of key COVID-19 mediators (ACE 2, TMPRSS2, and NRP-1) in male and female reproductive tissues may be linked to infertility issues following infection (Rajak et al., 2021). Additionally, the COVID-19 induced cytokine storm promotes heightened immune responses oxidative stress, and fever which may impair steroidogenesis, gametogenesis, and reproductive cycles in infected patients (Rajak et al., 2021). SARS-CoV-2 complicated pregnancies are reportedly more susceptible to adverse fetal outcomes such as intrauterine demise (Hcini et al., 2021). These observations align with the excessive viral load noted in infected placentas, particularly in ST cells and at the maternal-fetal interface (Argueta et al., 2021). Furthermore, a large influx of maternal immune cells, including macrophages, was observed in the intervillous spaces of infected placentas, predisposing tissue inflammation (Argueta et al., 2021). NRP-1 is highly localized within the ST cells, showing a greater affinity for infection than placental endothelial cells following exposure to SARS-CoV-2 or SARS-CoV-2 spike protein pseudo-typed lentivirus in placental culture ex vivo. However, infectivity was significantly diminished by blocking antibodies against ACE 2 and NRP-1 (Argueta et al., 2021). NRP-1 expression is upregulated in SARS-CoV-2 infected cells but not in uninfected cells (Cantuti-Castelvetri et al., 2020). The utilizing of NRP-1 receptors for SARS-CoV-2 entry may potentially hinder the physiological signaling action of NRP-1 in pregnancy, thereby dysregulating angiogenesis, Treg function, and possibly predisposing PE development.

Interestingly, NRP-1 facilitates SARS-CoV-2 entry via furin cleavage (Coutard et al., 2020). Furin is significantly upregulated during labor to serve as a prerequisite for inducing uterine contractions (Zhang et al., 2021). This increase in furin during normal delivery may be a risk factor for SARS-CoV-2 placental infection and vertical transmission due to high placental NRP-1 expression; however, there is a decline in NRP-1 expression as pregnancy progresses into the third trimester (Baston-Buest et al., 2011). Therefore, the risk associated with normal vaginal delivery during SARS-CoV-2 infection requires evaluation.

Reports of blood coagulation in SARS-CoV-2 infection were attributed to the release of inflammatory factors following endothelial injury (Machhi et al., 2020). Bechet et al., demonstrated an upregulation in tissue factors with subsequent vasoconstriction and thrombi formation following in vitro NRP-1 inhibition in tumor vasculature by a photosensitizing peptide [a chlorin conjugated with a heptapeptide (ATWLPPR)] (Bechet et al., 2010). Likewise, the competitive inhibition



**Fig. 3.** The role of NRP-1 in SARS-CoV-2 infection. Adapted from (Gudowska-Sawczuk and Mroczko, 2021; RayBiotech, 2021). Abbreviations: Coagulation factors, V/VIII domains (b1 and b2); Complement C1r/C1s, uEGF bone morphogenetic protein 1 (a1 and a2); Meprin, A-5 protein, and receptor protein-tyrosine phosphatase mu domain (MAM); PSD-95/Dlg/ZO-1 homology domain (PDZ); Receptor binding domain (RBD); Serine/Glutamate/Alanine sequence (SEA); Severe acute respiratory coronavirus 2 (SARS-CoV-2); Spike protein subunit 1 and 2 (S1 and S2).

**Table 1**  
Virus exploitation of NRP-1 for host cell entry.

Virus	Virus/Host NRP-1 Interaction	Refs.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	NRP-1 binds to the exposed C-terminal RRAR amino acid motif (residues 682–685) of the SARS-CoV-2 S1 subunit	Coutard et al. (2020); Balistreri et al. (2021)
Human T-cell lymphotropic virus type 1 (HTLV-1)	VEGF165 exon 8-like motif in the HTLV-1 surface protein (amino acids 90-94: KPXR) mediates direct binding to NRP-1 b1 domain and competes with VEGF165 for NRP-1 binding	Lambert et al. (2009)
Epstein-Barr virus (EBV)	EBV envelope fusion glycoprotein B (gB) directly interacts with the CendR binding region in the b1 domain of NRP-1. Residues involved: gB23-431, gB23-683 (ectodomain of EBV-gB) and gB23-853 (almost full-length EBV-gB)	Wang et al. (2015)

of VEGF ligands by the SARS-CoV-2 spike protein at the B1 domain of NRP-1 may induce endothelial dysfunction and systemic coagulation, similarly to PE (Bonnar et al., 1976; Mayi et al., 2021). Although an upregulation of NRP-1 facilitates endothelial cell adhesion and permeability as well as tightly regulates immune cell signaling and proliferation, its role in SARS-CoV-2 infection is yet to be elucidated (Siri et al., 2021). Furthermore, SARS-CoV-2 infected pregnant women exhibited

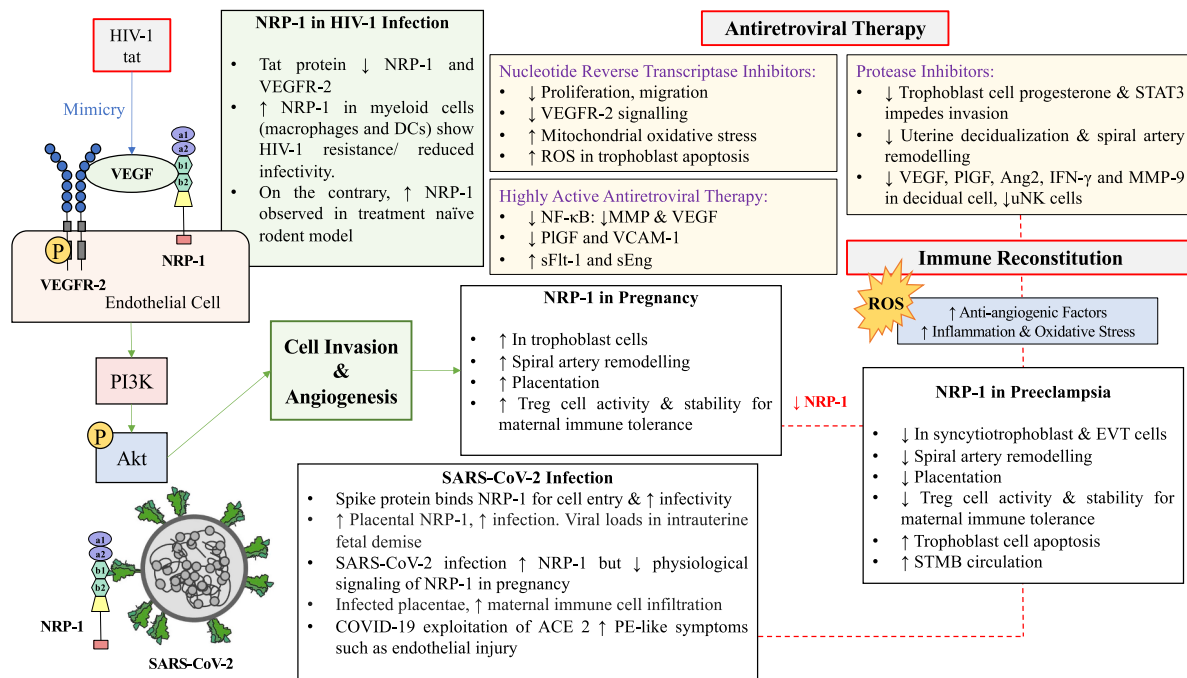
PE-like symptoms such as endothelial dysfunction and hypertension, associating COVID-19 with the onset and severity of PE (Naidoo et al., 2021).

A dysregulation of NRP-1 in pregnancy is a risk factor for PE, HIV-1 infection and SARS-CoV-2 infection. Fig. 4 explores HIV-1 infection, ART usage, and SARS-CoV-2 infection in the pathogenesis of PE.

### 9. The influence of microRNAs on neuropilin-1 in preeclampsia, HIV-1 infection and SARS-CoV-2 infection

MicroRNAs are non-coding RNA molecules comprising approximately 22 nucleotides (Bartel, 2018). They function in RNA silencing and post-transcriptional mediation of gene expression via complementary base-pairing with messenger RNA (mRNA) (Bartel, 2009; Fabian et al., 2010). MiRNAs achieve this by inducing mRNA cleavage, mRNA destabilisation by shortening their poly(A) tails and controlling the mRNA translation rate into ribosomal proteins (Bartel, 2009; Fabian et al., 2010). They target about 60% of the human genome and may serve as potential biomarkers for many diseases (Friedman et al., 2009). Since miRNAs offer fine-tuning of proteinsynthesis, imbalances in their expression may have pathological outcomes (Abel et al., 2021). A systematic approach was employed to isolate miRNAs regulating the NRP1 gene. Table 2 shows the regulation of NRP-1 in an environment where the identified miRNA is overexpressed. Moreover, Table 2 notes the expression status of the miRNAs in PE, HIV-1 infection and COVID-19.

MiRmap Web (<http://mirmap.ezlab.org>) is a comprehensive prediction of miRNA target repression strength. The target repression strength is determined by combining thermodynamic, evolutionary, and



**Fig. 4. Neuropilin-1 in PE, HIV-1 and SARS-CoV-2 infection.** Abbreviations: Angiotensin-converting enzyme 2 (ACE 2); CD4+ regulatory T cell (Treg); Coronavirus disease 2019 (COVID-19); Dendritic cells (DCs); Extravillous trophoblast (EVT); Human immunodeficiency virus type 1 (HIV-1); Interferon gamma (IFN- $\gamma$ ); Matrix metalloproteinase (MMP); Neuropilin-1 (NRP-1); Nuclear factor kappa B (NF- $\kappa$ B); Phosphatidylinositol 3-kinase (PI3K); Phosphate group (P); Placental growth factor (PlGF); Preeclampsia (PE); Protein kinase B (Akt); Reactive oxygen species (ROS); Severe acute respiratory coronavirus 2 (SARS-CoV-2); Signal transducer and activator of transcription 3 (STAT3); Soluble endoglin (sEng); Soluble fms-like tyrosine kinase-1 (sFlt-1); Syncytiotrophoblast microparticles (STBM); Trans-activator of transcription protein in HIV-1 (tat); uterine natural killer (uNK); Vascular cell adhesion molecule 1 (VCAM-1); Vascular endothelial growth factor 165 (VEGF165); VEGF receptor 2 (VEGFR-2).

**Table 2**  
MicroRNA regulation of NRP-1 and expression in PE, HIV-1 infection and COVID-19.

MicroRNA	Regulation of NRP-1 during $\uparrow$ microRNA	MicroRNA expression in PE	MicroRNA expression in HIV-1 infection	MicroRNA expression in COVID-19
miR-206	Downregulated (Xu et al., 2021)	Overexpressed (Sheng et al., 2020)	Overexpressed (Biswas et al., 2019)	None
miR-320	Downregulated (Zhu et al., 2020)	Overexpressed (Xie et al., 2019)	Repressed (Li and Chen 2018)	None
miR-365	Downregulated (Bai et al., 2015)	Overexpressed (Mori et al., 2016)	Overexpressed (Ramorola et al., 2021)	None
miR-181b	Downregulated (Cui et al., 2012)	Overexpressed (Miao et al., 2020)	Repressed (Hijmans et al., 2019)	None
miR-206	Downregulated (Xu et al., 2021)	Overexpressed (Sheng et al., 2020)	Overexpressed (Biswas et al., 2019)	None
miR-124-3p	Downregulated (Zhang et al., 2018)	Overexpressed (Tao et al., 2020)	Overexpressed (Farberov et al., 2015)	Repressed (Arora et al., 2020)
miR-199a-5p	Downregulated (Li et al., 2021a)	Repressed (Du et al., 2020)	Repressed (Fowler et al., 2016)	Repressed (Sardar et al., 2020)
miR-24	Upregulated (Kuai et al., 2021)	Overexpressed (Akgör et al., 2021)	Overexpressed (Squillace et al., 2014)	Repressed (Gambardella et al., 2021; Mone et al., 2021)
miR-200c	Downregulated (Vescarelli et al., 2020)	Overexpressed (Witvrouwen et al., 2021)	Repressed (Ramorola et al., 2021)	Overexpressed (Soltani and Zandi 2021)
miR-141	Downregulated (Ma et al., 2019)	Overexpressed (Ospina-Prieto et al., 2016)	Repressed (Kumar et al., 2019)	Overexpressed (Nersisyan et al., 2020)
miR-214	Downregulated (Chen et al., 2016)	Overexpressed (Kim et al., 2020)	Overexpressed (Squillace et al., 2014)	Overexpressed (Amini-Farsani et al., 2021)
miR-130a	Upregulated (Chen et al., 2016)	Repressed (Yang et al., 2015)	Overexpressed (Sharma et al., 2018)	Repressed (Li, et al., 2021)
miR-29b	Downregulated (Song et al., 2021)	Overexpressed (Xin et al., 2017)	Repressed (Chiang et al., 2012)	Overexpressed (Li, et al., 2021)

probabilistic factors as well as sequence-based features to predict possible binding regions and the ability of a given miRNA to hinder gene expression (Vejnar and Zdobnov, 2012). Using the MiRmap Web, this review further highlights the potential of identified miRNAs and their subgroups that bind and repress the NRP1 gene (Table 3).

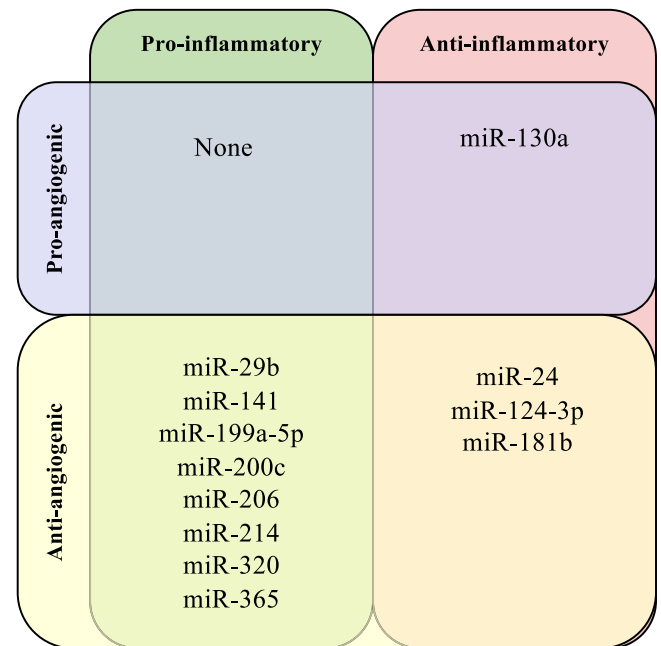
Previous literature highlights the inflammatory and angiogenic status of these miRNAs, seen in Fig. 5, which is central to their regulation in PE, HIV-1 infection and COVID-19. Table 2 demonstrates that four miRNAs (miR-200c, miR-141, miR-214, and miR-29b) are common to

pro-inflammatory conditions such as PE and COVID-19, implicating their role in evoking the immune response, similarly to their role in other inflammatory diseases (Reddy et al., 2012; Chen et al., 2020; Guo et al., 2021). Notably, these four miRNAs have been previously described as anti-angiogenic miRNAs (Zhao et al., 2017; Dong et al., 2019; Tang et al., 2020; Witvrouwen et al., 2021). Furthermore, anti-angiogenic miRNAs, miR-206, miR-320, miR-365, miR-181b, and miR-24 were overexpressed in PE; however, miR-181b and miR-24 were anti-inflammatory in previous studies (Wu et al., 2014; Fu et al., 2016;



**Table 3**  
MiRNAs' potential binding regions on the *NRP1* gene and repression strength.

MicroRNA	Potential Binding Regions on NRP-1	Individual MicroRNA Repression Strength (%)	MicroRNA Repression Strength (%)
miR-320b	(1) 33467229 (chr 10) 1775 (2) 33467870 (chr 10) 1134 (3) 33468799 (Chr 10) 205	(1) 42.97 (2) 72.58 (3) 94.87	93.85
miR-320a	(1) 33467229 (chr 10) 1775 (2) 33467870 (chr 10) 1134 (3) 33468799 (chr 10) 205	(1) 42.70 (2) 72.19 (3) 94.77	93.71
miR-320c	(1) 33467229 (chr 10) 1775 (2) 33467870 (chr 10) 1134 (3) 33468799 (chr 10) 205	(1) 41.80 (2) 70.09 (3) 94.84	93.47
miR-320d	(1) 33467229 (chr 10) 1775 (2) 33467870 (chr 10) 1134 (3) 33468799 (chr 10) 205	(1) 40.40 (2) 71.45 (3) 93.91	92.85
miR-124-3p	(1) 33467313 (chr 10) 1691 (2) 33467063 (chr 10) 1941 (3) 33468249 (chr 10) 755	(1) 29.03 (2) 73.13 (3) 94.06	92.32
miR-214-3p	(1) 33468313 (chr 10) 691 (2) 33467861 (chr 10) 1143	(1) 80.77 (2) 86.14	88.84
miR-206	(1) 33466460 (chr 10) 2544	(1) 93.04	85.95
miR-199a-5p	(1) 33468275 (chr 10) 729 (2) 33468324 (chr 10) 680	(1) 76.93 (2) 80.59	85.27
miR-24-3p	(1) 33468887 (chr 10) 117	(1) 92.07	84.61
miR-130a-3p	(1) 33466863 (chr 10) 2141	(1) 89.38	81.11
miR-141-3p	(1) 3366805 (chr 10) 2199	(1) 82.38	74.20
miR-320e	(1) 33468800 (chr 10) 204 (2) 33467871 (chr 10) 1133	(1) 53.78 (2) 56.46	65.56
miR-199a-3p	(1) 33467526 (chr 10) 1478	(1) 59.98	55.95
miR-181b-5p	(1) 33467977 (chr 10) 1027	(1) 54.44	51.43
miR-365b-3p	(1) 33467687 (chr 10) 1317	(1) 53.40	50.62
miR-365a-3p	(1) 33467687 (chr 10) 1317	(1) 53.40	50.62
miR-214-5p	(1) 33468915 (chr 10) 89	(1) 41.97	41.55
miR-200c-3p	(1) 33467446 (chr 10) 1558	(1) 23.84	26.22
miR-29b-2-5p	(1) 33466509 (chr 10) 2495	(1) 19.88	22.41
miR-141-5p	(1) 33468088 (chr 10) 916	(1) 6.21	7.89
miR-124-5p	(1) 33468337 (chr 10) 667	(1) 1.66	2.36



**Fig. 5.** The angiogenic and inflammatory status of identified microRNAs.

Liang et al., 2016; Xu et al., 2020; Green et al., 2021; Liu and Li, 2021; Wu et al., 2021; Yuan et al., 2021). The anti-inflammatory miRNAs (miR-24 and miR-130a) and pro-inflammatory miR-29b were repressed and overexpressed in COVID-19, respectively, consistent with their roles (Lorenzen et al., 2014; Zheng et al., 2016; Chen et al., 2020). MiR-124-3p was upregulated in PE but downregulated in COVID-19, possibly due to its anti-inflammatory properties rather than anti-angiogenic function (Tahamtan et al., 2018; Shi et al., 2020).

The pro-inflammatory MiR-141 is repressed in HIV-1 infection, possibly due to its immunocompromised state (Li et al., 2021b). The pro-angiogenic MiR-130a is suppressed in PE and COVID-19; however, miR-130a has great potential to suppress pro-angiogenic NRP-1 gene expression (repression strength: 81.11%) (Staszczak et al., 2011; Zheng et al., 2016). Pro-inflammatory miRNAs (miR-320, miR-199a-5p, miR-200c, miR-29b) were repressed, while anti-inflammatory miR-24 was overexpressed in HIV-1 infection due to reduced immunocompetence (Reddy et al., 2012; Lorenzen et al., 2014; Zhang et al., 2015; Chen et al., 2020; Liu and Li, 2021). Interestingly, these miRNAs are all anti-angiogenic, implicating the role of HIV-1 infection, particularly the involvement of tat, in angiogenic dysregulation (Chan et al., 2012; Wu et al., 2014; Tang et al., 2020; Xu et al., 2020; Witvrouwen et al., 2021). Although HIV-1 infection results in an immunocompromised state, overexpression of inflammatory miRNAs (miR-206, miR-365, and 214) and repression of miR-181b and miR-141 (anti-inflammatory miRNAs) may occur due to the immune reconstitution effect of ART and/or inconsistent data (Sun et al., 2012; Fu et al., 2016; Tooke et al., 2016; Wang et al., 2018; Guo et al., 2021; Li et al., 2021b; Wu et al., 2021). Pro-inflammatory miR-199a-5p displays repression across all three conditions, implicating therapeutic properties with dose-dependent transfection in infected individuals; however, an increase in miR-199a-5p may downregulate NRP-1 expression (Zhang et al., 2015).

NRP-1 may be downregulated by miR-320(a-d), miR-124-3p, miR-214-3p, miR-206, miR-199a-5p, miR-24-3p, miR-130a-3p and miR-141-3p with great repression strength (>70%); of which miR-320 and miR-141 are overexpressed in PE. Furthermore, miR-206 and miR-124-3p showed increased expression in PE and HIV-1 infection. Lastly, miR-214 is overexpressed in all three conditions, i.e., PE, HIV-1 infection and COVID-19. Therefore, it is plausible that treatment strategies promoting reduced levels of these miRNAs may upregulate and normalise NRP-1 expression.

## 10. Neuropilin-1 for therapeutic interventions in SARS-CoV-2 infection

The exploitation of NRP-1 for SARS-CoV-2 cell entry prompted studies to deter spike protein interaction at the b1b2 domain of NRP-1 (Chapoval and Keegan, 2021). A novel study observed a significant reduction of cell infection following pre-incubation of SARS-CoV-2 pseudovirus with recombinant soluble extracellular b1b2 domain of NRP-1 (Cantuti-Castelvetri et al., 2020). Several amino acid residues at the NRP-1 binding site (Y297, W301, N313, T316, P317, E319, D320, S346, E348, T349, K351, and Y353) have become a target of interest to block SARS-CoV-2 S1 interaction (Klaewkła et al., 2021; Charoute et al., 2022). Two monoclonal antibodies and a known NRP-1 antagonist molecule, EG00229, exhibited a considerable decrease in SARS-CoV-2 infection in cell culture by disrupting the interaction between the spike protein and the b1 domain of NRP-1 through high specificity binding of the NRP-1 CendR motif (Daly et al., 2020). Later comparisons highlighted that EG0137, R683G and A684M showed a greater affinity for the NRP-1 CendR binding region possibly due to interactions with more amino acid residues than EG00229 (Klaewkła et al., 2021). Furthermore, the R683G and A684M peptides also displayed a higher NRP-1 binding efficiency than the SARS-CoV-2 S1 CendR heptapeptide (Klaewkła et al., 2021).

The computational screening of five compounds showing potential against COVID-19 namely, Nafamostat, 5-[(E)-(hydroxyimino)methyl]-2-methyl-N-[(1R)-1-(naphthalen-1-yl)ethyl] benzamide (Y96), Selnexor, Ebastine and N-(4-methoxypyridin-2-yl)-2-(naphthalen-2-yl)acetamide (UGS) reveal lower NRP-1 docking scores ( $> -8.2$  kcal/mol) and more active key residue interactions than EG00229 and EG01377 ( $-6.6$  and  $-7.1$  kcal/mol, respectively (Charoute et al., 2022). A recent study by Katopodis et al., identified three miRNAs (miR-148a-3p, miR-152-3p and miR-148b-3p) that may effectively regulate both NRP-1 and a disintegrin and metalloproteinase 17 (ADAM17), a sheddase responsible for ACE 2 receptor cleavage to its soluble form for potential decoy of SARS-CoV-2 cell entry (Mulangu et al., 2019; Katopodis et al., 2022). Furthermore, miR-587 was common between NRP-1 and TLR4 (Katopodis et al., 2022). These findings provide a platform for effective COVID-19 treatment and clinical management.

## 11. Conclusion

NRP-1 is associated with the pathogenesis of PE, HIV-1 and SARS-CoV-2 infection. Various studies show dysregulated NRP-1 expression, which predisposes endothelial injury; therefore, an exacerbation of endothelial cell dysfunction and heightened immune responses would dominate in the synergy of these conditions. Post-transcriptional regulation of NRP-1 expression by miRNAs has been reported in PE, HIV-1 and SARS-CoV-2 infection. MiR-320 and miR-141 are overexpressed in PE, while miR-206 and miR-124-3p showed an increased expression in PE and HIV-1 infection. Additionally, miR-214 is overexpressed in PE, HIV-1 infection and COVID-19, implicating novel treatment strategies that reduce these miRNAs to upregulate and normalize NRP-1 expression.

## Future recommendations and clinical perspectives

Further studies are warranted to validate the influence of HIV-1 infection on NRP-1 expression. In light of the optimal conditions established following the incline in labor-induced furin in severe COVID-19 complicated pregnancies, an assessment of normal vaginal delivery as a risk factor of SARS-CoV-2 vertical transmission requires scrutiny. NRP-1-focused therapies for COVID-19, including miRNA suppression of NRP-1, are promising; however, the expression of miRNAs in conditions such as PE, HIV-1 infection and COVID-19 necessitates great examination during therapeutic transfection studies involving comorbidities. Moreover, inconsistencies in the data on miRNA regulation in PE, HIV-1

infection and COVID-19 require clarification.

## CRediT authorship contribution statement

**Nitalia Naidoo:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Jagidesa Moodley:** Supervision, Writing – review & editing. **Olive Pearl Khaliq:** Writing – review & editing. **Thajasvarie Naicker:** Supervision, Writing – review & editing.

## Declaration of Competing Interest

The authors declare no conflict of interest.

## Data Availability

No data was used for the research described in the article.

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