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Review

Angiogenesis, Lymphangiogenesis, and the Immune Response in South African Preeclamptic Women Receiving HAART

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Abstract: Purpose of the review: This review highlights the role of angiogenesis, lymphangiogenesis, and immune markers in human immunodeficiency virus (HIV)-associated preeclamptic (PE) pregnancies in an attempt to unravel the mysteries underlying the duality of both conditions in South Africa. **Recent findings:** Studies demonstrate that HIV-infected pregnant women develop PE at a lower frequency than uninfected women. In contrast, women receiving highly active anti-retroviral therapy (HAART) are more inclined to develop PE, stemming from an imbalance of angiogenesis, lymphangiogenesis, and immune response. **Summary:** In view of the paradoxical effect of HIV infection on PE development, this study examines angiogenesis, lymphangiogenesis, and immune markers in the highly HIV endemic area of KwaZulu-Natal. We believe that HAART re-constitutes the immune response in PE, thereby predisposing women to PE development. This susceptibility is due to an imbalance in the angiogenic/lymphangiogenic/immune response as compared to normotensive pregnant women. Further large-scale studies are urgently required to investigate the effect of the duration of HAART on PE development.

Keywords: angiogenesis; highly active anti-retroviral therapy; human immunodeficiency virus; lymphangiogenesis; immune response; preeclampsia

1. Problem Identification

Maternal Mortality and Hypertension in South Africa

The adoption of the Millennium Development Goals from 1990–2015 led to a decline in global maternal mortality by 44%; however, South Africa (SA) was unable to reach the target set by the United Nations (Millenium Development Goals, 2015 Report). South Africa has since embraced the Sustainable Development Goals 2016–2030 to reduce its maternal mortality ratio to <70 deaths/100,000 live births [1]. Despite a decline in maternal deaths from human immunodeficiency virus (HIV) infection and obstetric hemorrhage over the period 2008–2016, no change in mortality emanating from hypertensive diseases in pregnancy (HDP) occurred [2]. In fact, deaths from HDP is the commonest direct cause of maternal mortality as reported by the Confidential Report of Saving Mothers in 2017 [2]. Hypertensive diseases in pregnancy account for 18% of all maternal deaths in SA [3]. In developed

countries, HDP has a prevalence of 5–10% [4]; however, in developing countries, it occurs more frequently. The incidence of preeclampsia (PE) was 12% amongst all primigravidae who delivered at a large regional hospital in SA [5]. In SA, PE significantly affects both the mother and perinatal morbidity and death. The World Health Organization (WHO) reported that this multisystem pregnancy disorder accounts for 1.6% of maternal deaths in developed countries [6] and 1.8–16.7% in developing countries such as South Africa, Egypt, Tanzania, and Ethiopia [7,8].

2. Human Immunodeficiency Virus Infection in South Africa

HIV infection is a grave public health challenge globally. Sub-Saharan Africa constitutes 56% of the HIV-infected global population [9]. In 2017, women accounted for a disparate 59% of new adult HIV infections (>15 years) [10]. In SA, 13.1% of the total population is HIV-positive, of which 20% involves women in their childbearing age (15–49 years) [11]. Greater than 40% of the global HIV-infected population includes adults residing in the region of KwaZulu-Natal (KZN) [9]. Moreover, the Antenatal HIV and Syphilis Surveillance Report indicates that >37% of antenatal attendees in KZN province are infected [12]. Hence, healthcare professionals providing maternity care are challenged with a double burden of HIV infection and HDP.

The association between HIV infection and PE emanates from the different immune responses [13]. In light of the pervasive nature of both conditions in KZN, this association warrants urgent investigation. Notably, in SA, our group performed extensive research on the effect of angiogenesis and lymphangiogenesis in HIV-infected PE women. Therefore, this review serves to highlight the effect of pregnancy type and HIV status on angiogenesis and lymphangiogenesis using South African cohorts. We also provide compelling evidence of the mechanism(s) that HIV utilizes to exploit the angiogenic system. Furthermore, we provide data based on highly active anti-retroviral treatment (HAART) on reconstituting the immune system and its influence on PE development.

3. Angiogenesis

Angiogenesis is defined as the migration, development, and differentiation of endothelial cells to form new blood vessels [14]. It is initiated by pro-angiogenic vascular endothelial growth factors (VEGFs) and placental growth factors (PlGFs), which increase vessel permeability and promote proteolysis of the extracellular matrix via proteases, resulting in endothelial cell proliferation. Thereafter, endothelial cells migrate and invade the lumen, followed by endothelial maturation [15,16].

In normal pregnancy, the need for increased blood supply to the fetus is met by the physiological transformation of spiral arteries in both the decidua and myometrium. In contrast, as a result of deficient trophoblast invasion, spiral artery remodeling is restricted to the decidua in PE [17] and is often associated with adverse birth outcome.

Angiogenesis is also dysregulated in HIV-1 infected patients [18]. Notably, adverse birth outcome is elevated upon receipt of anti-retroviral therapy (ART) compared to HIV-uninfected women [19,20]. Since SA has the largest anti-retroviral rollout in the world, it is important to recognize any link(s) between HAART usage in pregnancy and the risk for PE development. In a novel study, Powis et al. (2013) assessed angiogenesis in preeclamptic women that initiated HAART during pregnancy [21]. They demonstrated that women who developed PE had an upregulation of anti-angiogenic factors prior to HAART usage. Moreover, a recent report correlated altered angiogenesis with ARV usage in the second and third trimesters as a progenitor of preterm birth, small for gestational age, and stillbirth [22].

3.1. Soluble Fms-Like Tyrosine Kinase 1 (sFlt1), Placental Growth Factor (PlGF), and Soluble Endoglin (Eng)

It is well documented that placental sFlt1 is elevated in PE, resulting in a rise in systemic levels with a concomitant decline in VEGF and PlGF [23]. The anti-angiogenic factor sFlt-1 is a scavenger receptor for VEGF and PlGF, thereby dampening their constructive effects on the maternal endothelium [24]. Moreover, in pregnant rats, the administration of sFlt1 induces the clinical symptoms of PE [25]. Flt-1 and sFlt-1 levels in the placenta are upregulated in PE compared to controls, irrespective of

HIV infection [26]. Working in our laboratory, Govender et al. (2013) demonstrated increasing levels of serum sFlt1 and sEng in PE, regardless of HIV infection [27]. sFlt1 and sEng are implicated in the endothelial dysfunction of PE. Moreover the downregulation of serum sFlt1 and sEng within HIV-infected women advocates counterbalance of the immune hyperactivity in PE [27]. sEng weakens the binding of TGF-β1 to its receptors and blocks the activation of the endothelial nitric oxide synthase 3 (eNOS) pathways downstream, thereby inducing hypertension [28]. The recent use of sFlt-1:PlGF ratio for the clinical prediction of severe early-onset PE is encouraging [29].

3.2. Vascular Endothelial Growth Factor (VEGF)

The permeability of blood vessels is enhanced by VEGF, thereby inducing angiogenesis and vasculogenesis [30]. The VEGF family comprises VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF [31]. VEGF receptors include VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR) [31]. VEGF-A and VEGF-B bind to VEGFR-1 (Flt-1); however, in PE, binding is blocked by the antagonist sFlt-1 or sVEGFR-1, a spliced soluble variant of VEGFR-1 [32]. VEGFR-2 is an antagonist to VEGF and increases arterial pressure [33]. Both VEGF-C and VEGF-D bind to VEGFR-3, thus expediting lymphangiogenesis [34].

3.3. Platelet Endothelial Cell Adhesion Molecule 1 (PECAM-1)

Vascular development is influenced by PECAM-1 through the formation of a complex with VEGFR-2 and VE cadherin [35]. In PE, PECAM-1 induces neutrophil and platelet activation, thereby promoting vascular damage [36]. Thakoordeen et al. (2017) demonstrated a similar level of PECAM-1 between control and preeclamptic pregnancies ($p = 0.07$), while no correlation was found based on HIV infection ($p = 0.68$) or across study groups ($p = 0.24$) [37].

3.4. Angiopoietin (Ang)-2

The angiopoietin family includes Ang-1, Ang-2, Ang-3, and Ang-4 types, which are vital for embryonic angiogenesis. These growth factors are ligands for the vascular endothelial receptor tyrosine kinase (Tie-2), required for vascular activation [38]. Mbhele et al. (2017) demonstrated that, in contrast to PlGF, increased levels of Ang-2 and Eng were noted in PE. The gestational period (early- or late-onset PE) had no effect on Ang-2 expression; yet, it was associated with Eng ($p < 0.0001$) and PlGF ($p = 0.0033$). HIV infection did not affect Ang-2 ($p = 0.4$), Eng ($p = 0.4$), and PlGF ($p = 0.7$) levels [39].

3.5. sTie-2

During development, vascular endothelial cells express the transmembrane tyrosine kinase receptors Tie-1 and Tie-2, which are responsible for vascular maturation and angiogenesis [40]. Angiopoietin-1 via Tie-2 signaling facilitates endothelial development, whilst Ang-2 acts as an Ang-1 antagonist by binding to the Tie-2 receptor [41].

However, whilst vessel growth is dependent on Tie-2 [19], Tie-2 may be proteolytically cleaved to produce sTie-2. This soluble form inhibits Tie-2 signaling by averting angiogenesis [19,20]. Mazibuko et al. (2019) demonstrated that soluble Tie-2 levels were dissimilar between preeclamptic and control pregnancies ($p = 0.0403$). In contrast, HIV status did not affect sTie2 and soluble human epidermal growth factor receptor 2 (sHER2) manifestation [42]. Also, HER2 is a membrane-bound receptor tyrosine kinase that is shed via proteolytic cleavage into body fluids [43]. Mazibuko et al. (2019) reported that sHER2 levels were similar between pregnancy types (control *vs.* PE; $p = 0.3677$), regardless of HIV status ($p = 0.5249$). These results may be due to the hypoxic pro-oxidative milieu of both PE and HIV infection, as sHER2 interferes with mitogen-activated protein kinase (MAPK) and Phosphatidylinositol-3-kinase/ protein kinase B (P13K/Akt) signaling [42].

3.6. Vascular Endothelial Growth Factor and HIV Tat protein

The accessory protein Tat of HIV-1 interferes with intracellular function by evading host response mechanisms, and may, therefore, contribute to the high inflammatory reaction in HIV-infected PE [44]. The Tat protein is a trans-activator of viral gene expression and is released extracellularly during HIV acute infection [45]. Since Tat has a similar arginine- and lysine-rich sequence to VEGF, it is recognized as a powerful angiogenic factor [46]. Tat imitates VEGF by attaching to and stimulating Flk-1/KDR [47]. Tat promotes endothelial cell adhesion through the binding of its arginine–glycine–aspartic acid region to the $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrins and VEGFR-2/KDR via its basic domain [46]. Also, a combined Tat/FGF-2 effect is attributed to fibroblast growth factor (FGF-2), which induces the expression of the $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrins, which aids Tat binding [48].

Additionally, HIV-1 via gp120 binds to heparin sulphate proteoglycans (HSPG) on endothelial cells, amplifying viral infectivity and thereby expediting the release of Tat [49]. Tat induces endothelial cells to migrate, adhere, and grow as a capillary-like network in vitro [50]. HIV Tat was also shown to bind F1k-1/KDR, one of the receptors for VEGF, suggesting an additional mechanism for Tat to exert its angiogenic effect [47].

Defective cell signaling by the Tat protein alters endothelial cell morphology, gene expression, and survival by stimulating the MAPK pathway. The movement from the gap 0 to gap 1 (G0 to G1) phase of naïve T cells enables productive HIV infection [51]. The HIV-1 Tat protein facilitates MAPK activity by promoting a change from the G0 to G1 phase of naïve T cells, thereby stimulating HIV infection [51].

4. Lymphangiogenesis

Lymphatic vessels were first described in the 17th century and consists of a vascular-like network. They play a pivotal role in maintaining tissue fluid homeostasis, transport of proteins, macromolecules, and cells such as leucocytes and activated antigen-presenting cells for immune protection [52]. This vascular-like network consists of a monolayer of blind-ended capillaries transferring "lymph" to the collecting lymphatics. The expansion of new lymphatic vessels from pre-existing ones, called lymphangiogenesis, is controlled mainly by growth factors, i.e., VEGFs such as VEGF-C and its ligand VEGFR-3, VEGF-D [53–55], and other factors, i.e., hypoxia-inducible factor 1-α (HIF-1α), the Tie/angiopoietin system, neuropilin-2, and integrin-α_9 [56–61]. However, until recently, there was a paucity of data on the lymphatic profile during pregnancy and in PE [62–64].

4.1. Lymphatic System in the Placenta

The human placenta is an hemochorial organ and is highly vascularized; yet, there are conflicting reports on the presence of lymphatic vessels in the placenta. However, Gu et al. (2006) [65], Wang et al. (2011) [66], and Liu et al. (2015) [67], as well as our recent observations [68], do not confirm the presence of lymphatic vessels in the placenta. The aforementioned groups instead observed a stromal network immunostained with podoplanin. Lymphangiogenesis was observed at the decidua [68–72] and the uterine wall [64,73].

4.2. Lymphangiogenesis and Preeclampsia

In PE, a dysfunctional fluid clearance manifests as an excessive accumulation of interstitial fluid causing edema [74]. B cells, macrophages, and reticular stromal cells activate the production of VEGF A, C, and D, thereby affecting signaling pathways for the induction of lymphangiogenesis [74]. Increased lymphangiogenesis (pro VEGF-C) is a compensatory response to the heightened exaggerated inflammatory state of PE [75,76]. Indeed, VEGF induces lymphangiogenesis [65]. Nevertheless, Shange et al. (2017) reported no significant difference between VEGF-C and D from PE mothers and control [74]. This upregulation of VEGF-C in PE was observed in early-onset PE; however, one needs to note that patients were on dual ARV therapy [73].

Furthermore, hypoxia-inducible factor-1 (HIF-1) plays an important role in the pathogenesis of PE, and indirectly enhances the molecular regulation of VEGF [66,67,77]. The upregulated *HIF-1* gene plays a critical role in the pathogenesis of PE [58,78–80] and contributes to the lymphangiogenesis in PE.

4.3. Lymphangiogenesis and HIV Infection

At the mucosal level, HIV-1 uses endothelial cell co-receptors CXCR4 and CCR5 before disseminating through lymphatic endothelial channels to the lymph nodes and, thereafter, moving into the general blood circulation. HIV infection plays a crucial role in lymphatic development; nevertheless, its functional integrity is complex and not fully understood. Three HIV-1 proteins, notably the envelope glycoprotein (gp120), transactivator of transcription (Tat), and the matrix protein (p17), may contribute to HIV-associated vascular disorders. HIV-1 gp120 induces apoptosis in endothelial cells. Tat triggers angiogenesis by using the matrix protein p17 [81] to stimulate the endothelin-1/endothelin B receptor axis [82], thereby activating the protein kinase Akt and extracellular signal-regulated kinase (ERK) signaling pathways [66,77,82,83].

The secretory protein (Slit2) and its receptor roundabout protein (Robo4) expressed on endothelial cells also serve to modulate endothelial cell permeability and, hence, have a determinant participation in the pathophysiological mechanism of lymphangiogenesis [84]. Although Slit2/Robo4 interactions are not fully elucidated, a previous study reported an inhibition of VEGF-C and a blockage of VEGFR-3 [85]. Additionally, HIV-1 gp120 leads to hyperpermeability of lymphatic cells in vitro via modulation of fibronectin expression and activation of $\alpha_5\beta_1$ integrins. On the other hand, Slit2 blocks the interaction between $\alpha_5\beta_1$ and Robo4, thus inhibiting lymphatic hyperpermeability [81].

This results in an imbalance of the Akt and ERK signaling pathways, which leads to dysregulation of lymphangiogenesis in PE, since it was shown that, during the pathophysiology of PE, there is decreased P13K/Akt signaling [86].

4.4. Lymphangiogenesis in the Duration of HAART and the Risk of Preeclampsia

By enhancing pro-inflammatory cytokines and chemokines, HIV-1 infection mimics PE, thereby influencing the prevalence of PE among HIV positive women. The HAART intervention improves endothelial function and decreases the inflammatory milieu of PE. However, that is not evident, as the timing and duration of the HAART is not clear in most the studies. Despite long-term use of HAART improving mortality among HIV positive patients, the morbidity (particularly vascular and metabolic in nature) is still a serious concern [87]. Two HIV-1 proteins seem to undermine the beneficial action of HAART in the restoration of endothelial cell (EC) function: HIV-1 Tat and matrix protein p17, which impair the endothelial cells. A recent study on HAART showed that angiogenesis and lymphangiogenesis are downregulated with Nucleoside reverse transcriptase inhibitors (NRTIs) by inducing mitochondrial oxidative stress and subsequently impairing receptor tyrosine kinase (RTK) signaling in EC [88], suggesting that NRTIs might trigger the development of PE.

The prevalence of PE in HIV-infected pregnancies is lower; however, upon HAART administration, the risk of PE development increases [13,89]. The association between lymphangiogenesis in the duration of HAART and the risk of PE development is unclear; hence, more research on lymphangiogenesis at the maternal and fetal interface is vital, particularly in immune transfer and ARV usage.

5. Highly Active Anti-Retroviral Therapy

Protease inhibitors (PI) induce the progression of Kaposi sarcoma [90]. PIs are potent anti-angiogenic factors that block FGF action [91]. PIs deter HIV aspartyl protease and, hence, the production of HIV virions, thus promoting immune restoration. Also, glucose transporter (GLUT)-4, inhibits glucose uptake and affects the cellular proteasome by triggering p53 protein intracellular accumulation, resulting in apoptosis. Finally, the functional impairment of activator protein (AP)-1, specificity protein (SP)-1 or

nuclear factor kappa b (NF-κB) transcription factors leads to a decline in MMP and VEGF expression, thereby preventing angiogenesis.

Anti-retroviral drugs regimens are associated with the development of metabolic disorders such as insulin resistance, dyslipidemia, impaired glucose tolerance, and abnormal body fat distribution, which predispose HIV-infected individuals to cardiovascular-related diseases [92]. Anti-retroviral therapy was also shown to lead to endothelial dysfunction [93,94] and decreased nitric oxide, ultimately resulting in induced endothelial oxidative stress [95], which is similarly observed during the pathophysiology of PE [96]. It is, therefore, possible that predisposition to PE may result from endothelial dysfunction and reduced nitric oxide synthase induced by HAART exposure.

Although some studies report on the endothelial HAART-induced endothelial dysfunction, conflicting reports exist. A study done by Torriani et al. (2008) showed improved endothelial function after ARV administration [97]. Additionally, Savvidou et al. (2011) found normal placental perfusion among HIV-infected women, with uncomplicated pregnancies, receiving and not receiving HAART [98]. In contrast, a study done by Sebitloane et al. (2017) evaluating the effect of HAART on HDP showed that, among all women with HIV, a greater risk of mortality due to HDP was reported among those who received HAART compared with those who did not [99].

6. Immune Maladaptation

6.1. Natural Killer Cells in Normal versus Preeclamptic Pregnancies

Natural killer (NK) cells are dysregulated in the presence of preeclampsia and HIV infection. In normal pregnancy, these cells promote placental development by balancing the immune response at the maternal–fetal interface [100]. The function of NK cells is controlled by inhibitory receptors [101] and activating receptors, C-type lectin receptors, and Ig-like receptors (2B4)] [102–104].

During normal pregnancy, the interaction between the maternal NK cells and fetal cells is controlled by NK cell inhibitory receptors, which prevents inadequate trophoblast invasion. However, this action is prevented in PE pregnancies since activating receptors are predominant, leading to shallow trophoblast invasion [105]. Similarly, the function of NK cells during HIV infection is downregulated or similar to NK cells in a healthy pregnancy state [106]. A study conducted by Mela and Goodier showed reduced activation peripheral NK cells of HIV-infected individuals [107].

6.2. Role of HAART on NK Cells and Risk of Preeclampsia Development

Natural killer cells play a role in controlling HIV [108] and are also reported to play a role in pregnancy complications such as miscarriage, implantation failure, and PE development [109–111]. In the duration of HAART, NK cells control HIV by secreting CC chemokines. These chemokines inhibit HIV replication via activation of non-cytolytic mechanisms [112]. Several studies reported on the influence of changes that may occur on NK cells in the duration of HAART exposure, and found conflicting results. A study by Valentin et al. (2002) reported higher frequency of NK cells after HAART initiation [113]. Similar findings were shown by Ballan et al. (2007) and Michaelsson et al. (2008) [114,115]. In contrast, a study done by Fria et al. (2015) examining the HAART effect on T-cell recovery versus NK cells found low NK subset recovery after HAART exposure when compared with T-cell recovery during the early months of therapy [116], suggesting that HIV infection of NK cells is important for viral persistence [113].

NK cells are also implicated in pregnancy complications; it was documented that NK cell activation may lead to inadequate trophoblast invasion and may result in exaggerative immune response, which is commonly associated with PE development [117]. Therefore, the possible mechanism responsible for PE development in HIV-infected women might be due to T-cell activation rather than NK cell subset recovery. More studies are needed to confirm how NK cells are regulated in the duration of HAART in order to understand the pathogenesis of PE in HIV-associated pregnancies.

7. Cytokines in Normal Pregnancy, Preeclampsia, HIV Infection, and in the Duration of HAART

7.1. T Helper Cell 1 and T Helper Cell 2 (Th1 and Th2)

During normal pregnancy, anti-inflammatory (Th2) cytokines are predominant [118], whereas, during the pathogenesis of PE, pro-inflammatory (Th1) cytokines are predominant [119]. However, during the progression of HIV infection, Th2 cytokines are predominant (Figure 1) [120,121]. HIV-infected pregnant women on HAART present a shift toward Th1 immune response [122]. Therefore, HIV-infected pregnant women on HAART have increased risk of developing PE [123].

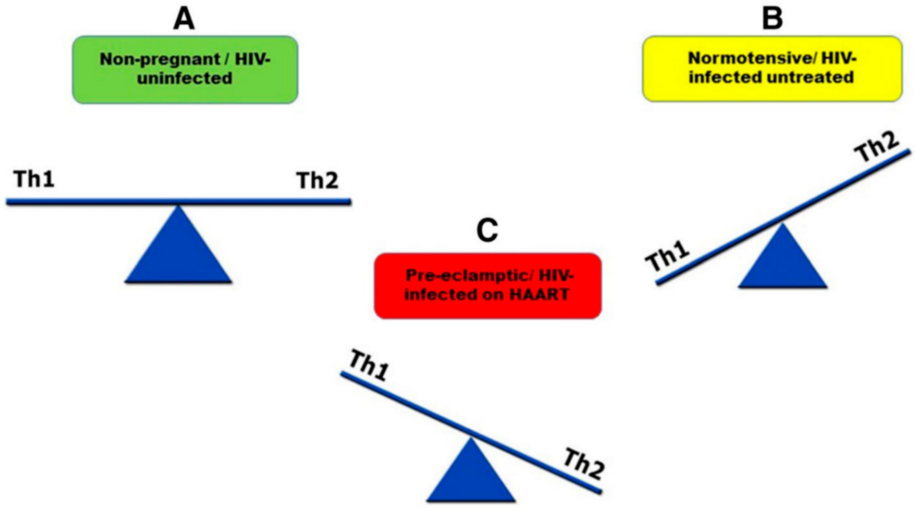

Figure 1. Schematic diagram representing how pro-inflammatory (Th1) and anti-inflammatory (Th2) cytokine are regulated in **A** non-pregnant or HIV-uninfected, **B** normotensive or HIV-infected untreated and **C** pre-eclamptic or HIV-infected on HAART. **A** Shows a balance in the distribution of Th1 and Th2. In **B** there is an imbalance of cytokines with more Th2 release than Th1. This imbalance increases of HIV infection in untreated women. In **C** Th1 levels are higher than Th2. HAART induces Th1 response and leads to pre-eclampsia development [123].

7.2. T Helper Cell 17 (Th17) and T Regulatory Cells (Treg)

Immune cells involved in pregnancy extend from Th1/Th2 into the Th1/Th2/Th17 and regulatory T cells (Treg), introducing Treg as regulators of Th17 lymphocytes and other immune cell types involved in placental development and maintenance [118,124].

Th17 cells are characterized by the secretion of IL-17/IL-17A and are also associated with inducing Th1 cytokine production. An upregulation of Th17 cells is associated with the pathophysiology of autoimmune, chronic inflammatory diseases, allergic disorders, and graft-rejection reactions [125]. Furthermore, it was reported that Th17 cells are upregulated in PE compared to normotensive pregnancies [126,127] and downregulated during the progression of HIV infection [128]. Currently, no studies investigated how IL-17A is regulated in the presence of both PE and HIV infection; more studies are needed in order to have a better understanding of how this cytokine is regulated in the pathophysiology of both conditions, especially in the duration of HAART.

Regulatory T cells are another type of lymphocytes involved in the pathophysiology of PE. In pregnancy, upregulation of these cells is important for maintaining normal pregnancy development [129–131]. Downregulation of Treg cells was reported in PE [132].

In the presence of HIV infection, the frequency of Treg cells is increased, implying their role in the progression of the disease [133–135]. In the duration of HAART, the frequency of Treg cells was shown to be decreased or similar to that of HIV-uninfected individuals [136,137]. Currently, there are no studies that investigated how Treg cells are regulated in the presence of both PE and HIV infection. Therefore, more studies are needed in order to improve management of PE in the presence of HIV

infection, and in order to have a better understanding of the pathophysiology of PE in the presence of HIV infection.

8. Conclusions

This paper elaborated on the paradigm shift of HIV's effect on angiogenesis in normotensive and preeclamptic pregnancy. Whilst an imbalance in the angiogenic and lymphangiogenic transference predominates in PE, we highlight the parodist effect of HIV as it utilizes its accessory proteins to exploit VEGF's effect. Furthermore, due to the ubiquitous nature of HIV infection in South Africa, this paper also outlines the effect of HAART on the risk of PE development, albeit not on the duration of the therapy. Current literature is controversial on the effect of HAART on T-cell reconstitution, with regard to NK cell subset recovery and the influence of Th1/Th2/Th17 and Treg cell dysregulation during HIV infection in pregnancy. Since cytokine stimulation is disparate in HIV infection, PE, and during ARV usage, it is important that future research outlines the archetypal effect in pregnancy. Finally, this will improve therapeutic interventions in HIV-associated preeclamptic pregnancies, thus reducing maternal and fetal morbidity and mortality.

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Abbreviations

Ang-1	Angiopoietin-1
Ang-2	Angiopoietin-2
Ang-3	Angiopoietin-3
Ang-4	Angiopoietin-4
AP-1	Activator protein 1
ARV	Anti-retroviral therapy
CD94	Cluster of differentiation 94
CTLA-4	Cytotoxic T-lymphocyte antigen 4
CXCR1	Chemokine (C–X–C motif) receptor 1
CXCR2	Chemokine (C–X–C motif) receptor 2
ENOS	Endothelial nitric oxide synthase
FGF-2	Fibroblast growth factor
FIK-1	Vascular endothelial growth factor receptor 2 (VEGFR22, kinase domain receptor)
FOXP3	Forkhead box P3
Gp120	Glycoprotein 120
HIF-1	Hypoxic-inducible factor 1
HAART	Highly active anti-retroviral therapy
HDP	Hypertensive disorders of pregnancy
HELLP	Hemolysis, elevated liver enzymes, and low platelets
HIV	Human immuno-deficiency virus
IL-17	Interleukin-17
KDR	Kinase insert domain receptor
KIR2DS	Killer-cell immunoglobulin-like receptor 2DS
KZN	KwaZulu-Natal
LAIR-1	Leukocyte-associated immunoglobulin-like receptor 1
LIR1	Leukocyte immunoglobulin-like receptor 1
MAPKs	Mitogen-activated protein kinases
MMP	Matrix metalloproteases
NF-κB	Nuclear factor kappa B
NKG2	Natural killer cell G2

NKG2C	Natural killer cell G2A
NKG2D	Natural killer cell G2D
NKp30	Natural killer cell precursor 30
NKp44	Natural killer cell precursor 44
NKp46	Natural killer cell precursor 46
PE	Preeclampsia
PECAM-1	Platelet endothelial cell adhesion molecule 1
PLGF	Placental growth factor
SEng	Soluble endoglin
SFlt1	Soluble fms-like tyrosine kinase 1
Slit2/Robo4	Slit/Roundabout (Robo)
Sp-1	Specificity protein 1
Tat	Transactivating regulatory protein
TGF-ß	Transforming growth factor beta
TIE1	Tyrosine protein kinase receptor 1
TIE2	Tyrosine protein kinase receptor 2
Th1	T helper cell type 1
Th2	T helper cell type 2
Th17	T helper type 17
Treg	Regulatory T cells
UNAIDS	United Nations Program on HIV/AIDS
VE cadherin	Vascular endothelial cadherin
VEGF	Vascular endothelial growth factor
VEGFR-1	Vascular endothelial growth factor receptor 1
VEGFR-2	Vascular endothelial growth factor receptor 2
VEGFR-3	Vascular endothelial growth factor receptor 3
WHO	World Health Organization

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