Endothelial Progenitor Cells Increase In Older HIV-Infected Patients Receiving Telmisartan

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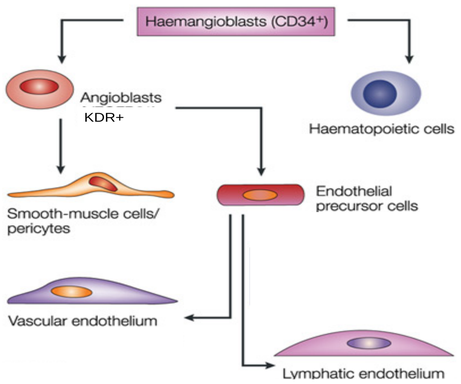
Poster # P=P6

Background

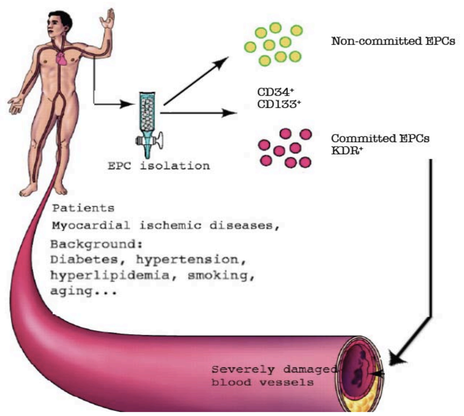
Endothelial progenitor cells (EPCs) are bone marrow-derived cells with angiogenic and vascular reparative capacity. EPCs can be measured by flow cytometry using markers of both cellular immaturity (CD34 and CD133) and endothelial commitment (KDR).



Adapted from Boshoff and Weiss. *Nature Reviews Cancer 2002;*2:373-382.

EPC production is partially mediated by angiotensin II and PPAR-Y, decreases with age and correlates with measures of vascular function and cardiovascular disease (CVD).[1,2]

Increased CVD risk and endothelial dysfunction are well documented in HIV infection,[3,4] but published EPC data is conflicting and limited to a few studies using varied EPC isolation techniques. Additionally, these studies were not limited to treated HIV infection or HIV+ persons with known CVD risk factors.[3,5-8]



Adapted from Murasawa S and Asahara T. *Physiology.* 2005;20:36-42.

Telmisartan is an angiotensin receptor blocker and PPAR-Y agonist that increases EPC production and decreases cardiovascular mortality in HIV- persons.[9-11] Renin angiotensin system blockade and PPAR-Y agonism lead to anti-inflammatory effects that are believed to promote EPC production independent of telmisartan's blood pressure-lowering effects.[12,13]

We prospectively assessed the effects of standard dose telmisartan on EPC number and type in older HIV+ patients on suppressive ART.

References

[1]Hill et al. N Engl J Med. 2003 Feb 13;348(7):593-600. [2]Schmidt-Lucke et al. PLoS One. 2010 Nov 3;5 (11):e13790. [3]da Silva et al. AIDS. 2011 Aug 24;25(13):1595-601. [4]Triant VA. J Clin Endocrinol Metab. 2007 Jul;92(7):2506-12. [5]Teofili et al. AIDS. 2010 Oct 23;24(16):2443-50. [6]Papasavvas et al. Antivir Ther. 2012;17(3):557-63. [7]Costiniuk et al. JID. 2012;205:713–7. [8]Gomez-Garre et al. J Acquir Immune Defic Syndr 2012;61:545–551. [9]Pelliccia et al. Atherosclerosis. 2010 Jun;210(2):510-5. [10]Endtmann et al. Hypertension. 2011 Sep;58(3):394-403. [11]Yusuf et al. N Engl J Med. 2008 Apr 10;358(15):1547-59. [12]Roks. Curr Op in Pharm 2011, 11:162–174.[13]Becher UM and Endtmann C. Curr Hypertens Rep (2011) 13:86–92. [14]Fadini et al. Circulation Research 2012, 110:624-637. [15]Blann et al. Thromb Haemost 2005; 93: 228-35.

Results

Methods

Study Design: Twelve-week, seventeen subject, open label, single arm trial of telmisartan 80 mg po daily.

Inclusion Criteria
- HIV+
- ≥50 years of age
- Plasma HIV-1 RNA <50 copies/mL on stable ART
- ≥1 traditional CVD risk factor (smoking, hypertension, hyperlipidemia, diabetes mellitus)

Data collection and processing
- Blood for EPC measurement was collected in the fasting state.
- EPCs were quantified via flow cytometry using fresh whole blood to optimize isolation.[14,15]
- EPCs were defined as viable $CD3^-/CD33^-/CD19^-$ cells that were also $CD133^+/KDR^+$, $CD34^+/KDR^+$, $CD34^+/CD133^+$ or $CD34^+/KDR^+/CD133^+$.[14,15]
- Clinical parameters, including blood pressure measurement, were performed using standardized protocols.

Statistical Analysis
- All analyses were exploratory.
- Absolute EPCs numbers are reported per 10^6 peripheral blood mononuclear cells (PBMCs).
- Median within-person six- and twelve-week EPC change scores are reported.
- EPC changes were also assessed as log-transformed values.
- Statistical significance was defined using the Wilcoxon rank-sum test (two-sided α=0.05).
- Spearman correlations were used to explore relationships between changes in EPCs and changes in clinical parameters.

Table 1: Baseline Characteristics

Subjects Enrolled	n=17
Gender	
Male	88% (15)
Female	12% (2)
Ethnicity	
African American	24% (4)
Hispanic	41% (7)
White	35% (6)
Age (years)	60 (54, 63)
BMI (kg/m^2)	27.1 (26.5, 30.2)
Tobacco use (current)	18% (3)
CD4 count (cells/μL)	625 (422, 725)
PI	71% (12)
Atazanavir	25% (3)
Atazanavir/ritonavir	25% (3)
Darunavir/ritonavir	25% (3)
Fosamprenavir/ritonavir	8% (1)
Lopinavir/ritonavir	17% (2)
NNRTI	29% (5)
Efavirenz	80% (4)
Nevirapine	20% (1)
NRTI	94% (16)
Abacavir	31% (5)
Lamivudine	31% (5)
Emtricitabine	63% (10)
Tenofovir	69% (11)
Zidovudine	6% (1)
Integrase Inhibitor (raltegravir)	29% (5)
Entry Inhibitor (maraviroc)	6% (1)
Glucose (mg/dL)	96.0 (91.5, 101.5)
Total cholesterol (mg/dL)	166.0 (144.0, 187.0)
Triglycerides (mg/dL)	108.5 (79.0, 141.0)
LDL (mg/dL)	94.0 (78.0, 111.0)
HDL (mg/dL)	43.7 (39.5, 52.2)
Diabetes[a]	12% (2)
Hypertension[a]	53% (9)
Hyperlipidemia[a]	71% (12)

Percent (n) or median with interquartile range.
[a]Defined as self-reported diagnosis or on-therapy at baseline.
BMI, body mass index; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

Figure 3: Twelve-Week Changes in EPC Number

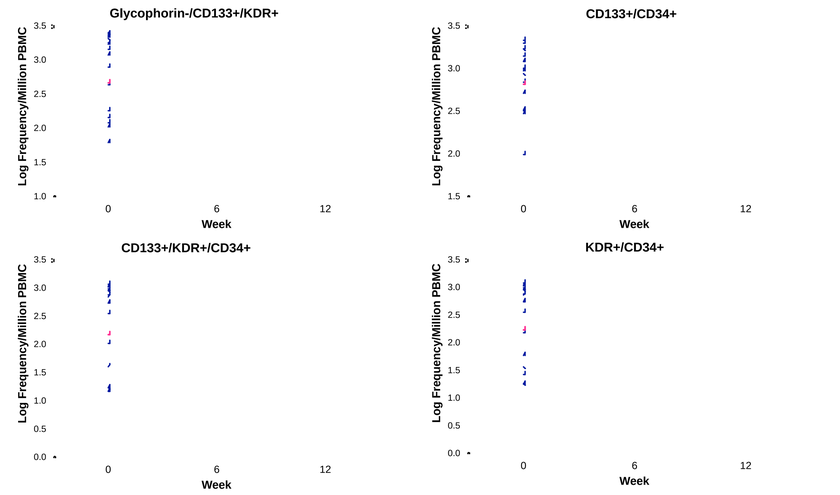
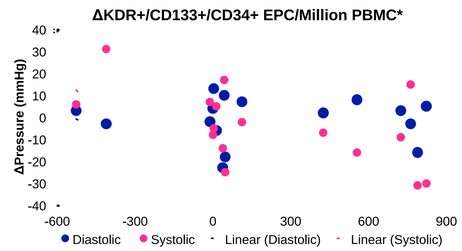


Figure 4: Relationship Between EPC Number and Blood Pressure



Twelve-week EPC changes correlated significantly with systolic but not diastolic blood pressure.
Systolic: R=-0.57, p=0.02
Diastolic: R=0.01, p=0.98

Figure 1: Gating Strategy for Flow Cytometric Putative EPC Analysis

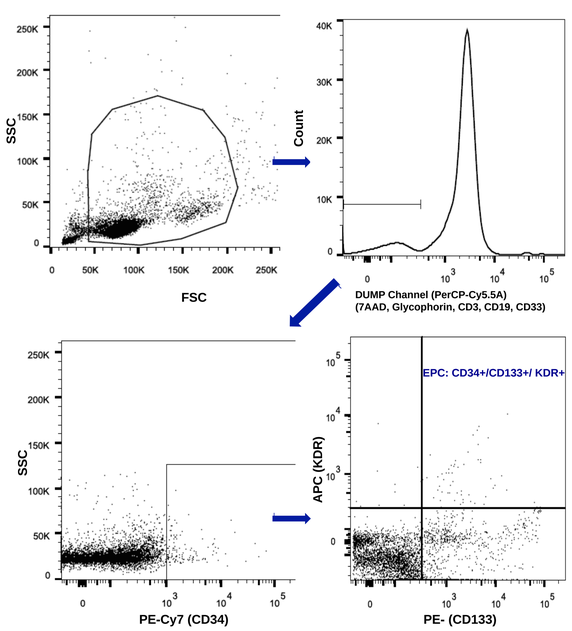
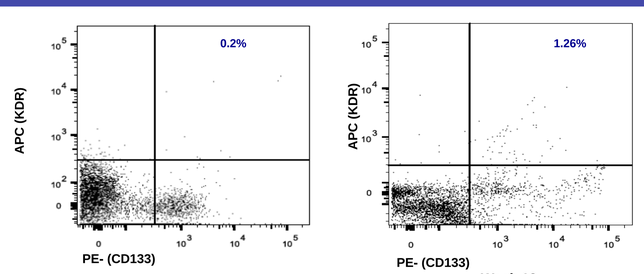


Table 2: Six- and Twelve-Week Changes in EPC Number

	Median # per 10^5 PBMC (IQR)			Median Within-Person Change (IQR)			
Total Absolute EPC	**Week 0**	**Week 6**	**Week 12*†**	**6 Weeks**	***p***	**12 Weeks*†**	***p***
$Glycophorin^-/CD133^+/KDR^+$	80 (27, 1124)	828 (113, 1882)	892 (176, 1599)	98 (10, 1194)	***0.02***	146 (-23, 1334)	*0.13*
$CD34^+/CD133^+$	333 (134, 855)	672 (316, 1218)	876 (312, 1285)	114 (-13, 254)	***0.06***	501 (60, 709)	***<0.01***
$CD34^+/KDR^+$	18 (08, 496)	395 (20, 852)	459 (41, 776)	23 (-14, 504)	***0.09***	56 (-03, 593)	***0.04***
$CD34^+/CD133^+/KDR^+$	9 (3, 480)	385 (16, 839)	441 (30, 746)	16 (0, 504)	***0.04***	45 (1, 640)	***0.02***
$CD34^-$ EPC Subset	**% of CD34+ EPC (IQR)**			**Median Within-Person Change (IQR)**			
$CD133^+$	349 (325, 464)	376 (317, 431)	364 (253, 417)	-4 (-27, 63)	*0.93*	-1 (-136, 141)	*0.98*
KDR^+	59 (17, 174)	148 (26, 260)	145 (49, 208)	27 (-2, 11.2)	*0.12*	-2 (-61, 69)	*0.71*
$CD133^+/KDR^+$	42 (4, 152)	144 (24, 254)	141 (31, 198)	26 (-1, 129)	***0.07***	4 (-60, 130)	*0.59*

*One subject excluded for increasing statin dose between weeks 6 and 12
†12 subjects off drug
IQR=Interquartile range

Figure 2: Twelve-Week $CD34^+/CD133^+/KDR^+$ EPC Changes



Summary & Conclusions

- **After twelve weeks, telmisartan increased endothelial regenerative potential (as measured by EPC number and immunophenotype) in older HIV+ adults on ART.**
- **All measured EPC immunophenotypes increased significantly, including $CD34^+/133^+/KDR^+$ EPCs, which are rare in circulation but highly specific for EPC lineage.**
- **Among $CD34^+$ EPCs, maturity markers (CD133+) remained stable, but endothelial commitment markers (KDR+) increased.**
- **The magnitude of $CD34^+KDR^+$ EPC increase was greater than previously reported in HIV- persons with coronary artery disease;[6] however, the clinical significance of this is unknown.**
- **EPC increases unexpectedly correlated strongly with declines in systolic blood pressure.**
- **Analysis of associations between changes in EPCs, inflammatory biomarkers and endothelial microparticle production is underway.**
- **Larger, randomized studies are needed to confirm these findings and define telmisartan's role as an agent for endothelial preservation in HIV+ adults.**

Acknowledgements

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