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AIDS 2009, **23**:645–650

Graves' disease following successful HAART of a perinatally HIV-infected 11-year-old

Graves' is an autoimmune disease in which antithyrotropin receptor antibodies are produced resulting in hyperthyroidism [1]. Clinical manifestations of hyperthyroidism include fatigue, weight loss, tachycardia, tremor, hyperreflexia, heat intolerance, sweating, irritability and lid retraction. Laboratory studies demonstrate low thyroid-stimulating hormone (TSH) (<0.02 mU/l) with elevated free thyroxin (T4) and tri-iodothyronine (T3) levels. Graves' disease in children is uncommon (1 : 5000) [2].

Immune reconstitution inflammatory syndrome (IRIS) occurs in HIV-infected individuals after the initiation of HAART [3–7]. The majority of IRIS cases in adults are associated with underlying viral infections and mycobacterium species [8]. These cases are considered early IRIS because they usually appear within 3 months of initiating HAART [5]. Hashimoto's thyroiditis and Graves' disease have been reported not earlier than 40 weeks after starting HAART and are considered late IRIS [5]. Graves' disease, after immune reconstitution from HAART, has been reported in a small number of adults with onset after initiation of HAART [3–7]. To our knowledge, there are no reports of HAART-associated Graves' in children.

An 11-year-old African–American male was diagnosed at the age of 9 years with perinatally transmitted HIV. Before therapy, his CD4 cell count nadir was 1 cell/μl and peak viral load 550 175 RNA copies/ml (Fig. 1). The patient was started and maintained on antiretroviral regimen comprising zidovudine/lamivudine and efavirenz. Viral load rapidly dropped and was undetectable within 2 months. The CD4 cell count rose, but at a slower rate, to 309 cells/μl (25.8%), 11 months after initiating therapy. The patient was compliant with medications and undetectable with a CD4 cell count of 689 cells/μl (31.3%) 2 years later. At 11 years of age, he presented with a 4-day history of fever, cough, congestion and heart palpitations and parent-reported weight loss that had occurred over a few weeks. At presentation, physical examination and chest radiograph findings were consistent with right upper lobe pneumonia, and it was believed his symptoms were due to this. The patient was treated with a 10-day course of oral antibiotics. At follow-up, he had resolution of cough and fever; however, weight loss and rapid heartbeat persisted. In addition, on review of symptoms, he reported sweating, feeling hot all the time, increased appetite and some fatigue. On physical examination, elevated heart rate (152 beats per minute), weight loss (2.5 kg over 2 months) and goitre were documented. No ophthalmologic abnormalities or family history of thyroid disease was found. Thyroid function tests showed decrease in TSH 0.07 mIU/ml (normal 0.37–6.0) and increase in T4 25 μg/dl (normal 4.5–12.0), T3 uptake 45% (normal 24–33%), free thyroxin index 11.3 (normal 1.2–4.9) and anti-TSH receptor antibody of 28 U/l (normal 0–1.5). Physical examination and laboratory findings were consistent with Graves' disease. The patient was started on propanolol and underwent thyroid ablation treatment with iodine-131. The patient had been enrolled into an investigational study in May 2003 that included measurements of an activation marker on $CD8^+$ cells, CD38. Activated $CD8^+CD38^+$ cells were markedly elevated from enrollment (6.5 months before Graves' diagnosis) through 2.5 months after diagnosis and then precipitously dropped (Fig. 1).

Graves' disease in HIV-infected adults is increasingly recognized as a late manifestation of IRIS. The prevalence of Graves' in the United Kingdom in HIV-infected adults is 2.4% in women and 0.2% in men [3]. The prevalence of Graves' in HIV-infected children is unknown. Our patient developed clinical manifestations of Graves' disease 30 months after starting antiretroviral therapy, coinciding with achieving plateau levels of CD4 cells. This is similar to findings in HIV-infected adults who develop Graves'; they are profoundly immunosuppressed before the start of HAART and showed good recovery of T cells prior to the onset of Graves' [3,6,9]. Unlike IRIS with opportunistic infections that usually develops in HIV-infected individuals during the first 3 months of HAART, Graves' disease in adults presents at a later time [3–6]. Some hypothesize that this delayed presentation is related to the timing of thymus-dependent generation of naive T cells [3,5]. It is unclear whether viral damage to the thymus or HAART-caused modulation of immune response results in the immune deregulation leading to Graves' in HIV-positive patients. It is possible that the predictable development of Graves' in a small fraction of individuals following initiation of HAART serves as a model for further unravelling the mechanisms of immune deregulation leading to Graves'. It is not possible to definitely attribute the occurrence of Graves' in HIV-positive patients to late IRIS. However, the association is inferred from the limited window after HAART initiation when Graves' is manifested, the relationship of recovery of $CD4^+$ lymphocyte numbers and Graves' onset. We found a high frequency of $CD8^+CD38^+$ cells

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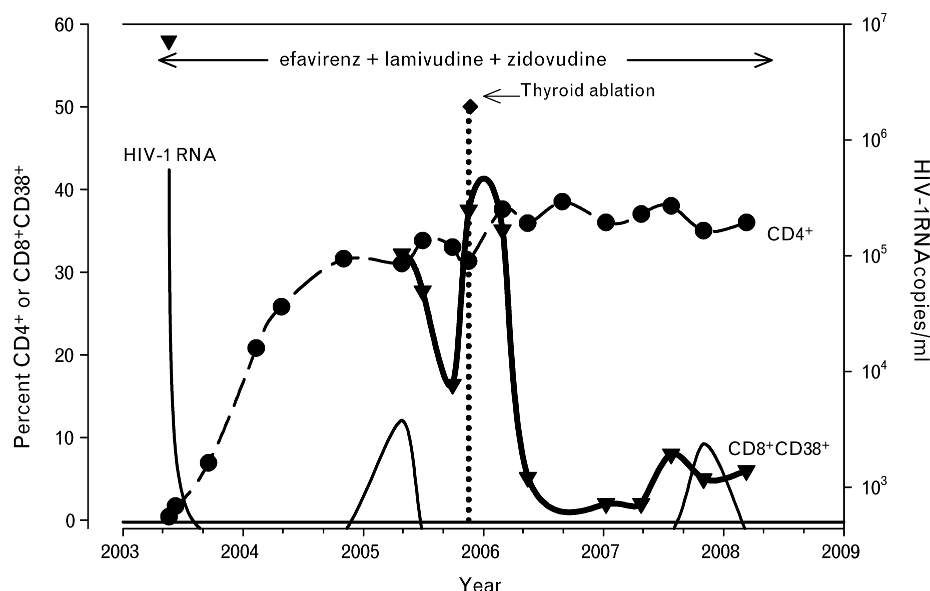

Fig. 1. Demonstration of elevated $CD8^+CD38^+$ cells preceding and coincident with the onset of Graves' disease in an HIV-1-infected 11-year-old. Levels of HIV-1 RNA (solid line, no symbols), CD4 cells (circles) and $CD8^+CD38^+$cells (triangles) relative to the onset of Graves' disease (vertical dashed line).

prior to the diagnosis of Graves' and during an interval when $CD4^+$ cells were more than 370 cells/μl and viral load was below the limit of detection (400 RNA copies/ml); an HIV disease status that is usually remarkable for low levels of activated $CD8^+$ cells [10–12]. French *et al.* [9] demonstrated increased sCD30, a marker of Th2 activation, in parallel with the onset of Graves' in an HIV-infected adult. Thus, the detection of T-cell activation in patients with well controlled HIV disease should trigger investigation into possible insipient autoimmune disease. Possibly, these markers will signal developing autoimmunity before full clinical disease is manifested.

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References

1. Pearce EN. **Diagnosis and management of thyrotoxicosis.** *BMJ* 2006; **332**:1369–1373.
2. Barnes HV, Blizzard RM. **Antithyroid drug therapy for toxic diffuse goiter (Graves disease): thirty years experience in children and adolescents.** *J Pediatr* 1977; **91**:313–320.
3. Chen F, Day SL, Metcalfe RA, Sethi G, Kapembwa MS, Brook MG, *et al.* **Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus (HIV) disease.** *Medicine (Baltimore)* 2005; **84**:98–106.
4. Hoffmann CJ, Brown TT. **Thyroid function abnormalities in HIV-infected patients.** *Clin Infect Dis* 2007; **45**:488–494.
5. Jubault V, Penfornis A, Schillo F, Hoen B, Izembart M, Timsit J, *et al.* **Sequential occurrence of thyroid autoantibodies and Graves' disease after immune restoration in severely immunocompromised human immunodeficiency virus-1-infected patients.** *J Clin Endocrinol Metab* 2000; **85**:4254–4257.
6. Vos F, Pieters G, Keuter M, van der Ven A. **Graves' disease during immune reconstitution in HIV-infected patients treated with HAART.** *Scand J Infect Dis* 2006; **38**:124–126.
7. Wong KH, Chow WS, Lee SS. **Clinical hyperthyroidism in Chinese patients with stable HIV disease.** *Clin Infect Dis* 2004; **39**:1257–1259.
8. Shelburne SA, Montes M, Hamill RJ. **Immune reconstitution inflammatory syndrome: more answers, more questions.** *J Antimicrob Chemother* 2006; **57**:167–170.
9. French MA, Lewin SR, Dykstra C, Krueger R, Price P, Leedman PJ. **Graves' disease during immune reconstitution after highly active antiretroviral therapy for HIV infection: evidence of thymic dysfunction.** *AIDS Res Hum Retroviruses* 2004; **20**:157–162.
10. Almeida M, Cordero M, Almeida J, Orfao A. **Relationship between CD38 expression on peripheral blood T-cells and monocytes, and response to antiretroviral therapy: a one-year longitudinal study of a cohort of chronically infected ART-naive HIV-1+ patients.** *Cytometry B Clin Cytom* 2007; **72**:22–33.
11. Flynn PM, Rudy BJ, Lindsey JC, Douglas SD, Lathey J, Spector SA, *et al.* **Long-term observation of adolescents initiating HAART therapy: three-year follow-up.** *AIDS Res Hum Retroviruses* 2007; **23**:1208–1214.
12. Resino S, Bellon JM, Gurbindo MD, Munoz-Fernandez MA. **CD38 expression in CD8+ T cells predicts virological failure in HIV type 1-infected children receiving antiretroviral therapy.** *Clin Infect Dis* 2004; **38**:412–417.

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Are defensin beta 1 gene polymorphisms associated with HIV infection and virus replication?

Three single nucleotide polymorphisms (SNPs) localized in the 5′-untranslated region (5′UTR) of the defensin beta 1 (*DEFB1*) gene (−52G/A, −44C/G, and −20G/A) encoding for the human beta defensin 1 (hBD-1) have been associated with the risk of HIV infection in two independent studies [1,2]. Recently, Baroncelli *et al.* [3] analyzed two of these 5′UTR *DEFB1* SNPs in 78 Mozambican HIV-infected women.

Here, we compare the results of the three studies [1–3] mentioned above with new findings obtained on two groups of Brazilian children (96 healthy controls, 47 boys, 49 girls, age 4.8 ± 3.2 years; 173 HIV-positive patients, 85 boys, 88 girls, age 5.1 ± 3.9 years) in order to elucidate the role of *DEFB1* functional SNPs in HIV infection. *DEFB1* SNPs genotyping was performed as previously described [1].

Braida *et al.* [1] and Milanese *et al.* [2] analyzed *DEFB1* SNPs in HIV-infected children (born from seropositive-naive mothers) and healthy children matched for age, sex and ethnicity. Braida *et al.* [1] studied an Italian population, whereas Milanese *et al.* [2] analyzed a Brazilian one, deriving from an admixture of African, Caucasian and native American populations [4].

Table 1 reports genotype and allelic frequencies of the 5′UTR *DEFB1* SNPs of Brazilian children included in this study and those observed by Braida *et al.* [1], Milanese *et al.* [2] and Baroncelli *et al.* [3] as well as the National Center for Biotechnology Information (NCBI) ones. Allele and genotype frequencies in the healthy controls of Braida *et al.* [1] are comparable with the European population reported by NCBI.

The frequencies of Brazilian healthy controls described by Milanese *et al.* [2] are similar to the new group of Brazilian healthy children and approximately intermediate between the European and African ones reported by the NCBI, as one should expect, given their ethnic background.

When considering HIV-positive patients, different results were achieved. Milanese *et al.* [2] found a significant increase ($P < 0.05$) of −52G/G and −20A/A genotypes in Brazilian HIV-infected children, suggesting an association with major susceptibility to infection.

Conversely, in the new group of Brazilian children analyzed, the frequencies of −52G/G and −20A/A genotype were not significantly different between healthy and HIV-positive children ($P > 0.05$) even if a trend towards a greater incidence of the −52G/G (60/173–35% in HIV-positive vs. 29/96–30% in healthy controls) and −20A/A (35/173–20% in HIV-positive vs. 11/96–11% in healthy controls) genotypes was evident. Significant differences in genotype and allele distribution could also be revealed by comparing Milanese *et al.*'s [2] HIV-positive population and this new one. For the −20G/A SNP genotype distribution, a *P* value of less than 1×10^{-05} was evidenced when comparing with HIV-positive patients in the two Brazilian populations using the chi-squared test. Genotype and allele frequencies were in Hardy–Weinberg equilibrium for the new Brazilian HIV-positive children, whereas those of Milanese *et al.* [2] were not.

In the Italian population, Braida *et al.* [1] showed a significant increase in the −44C/C genotype in HIV-positive patients when compared with healthy controls, as well as a slight increase in the −52A/A genotype, whereas the frequencies of the −20G/A polymorphisms remain the same in the two groups. All these findings indicate that *DEFB1* polymorphisms' role seems to vary in different populations and also within the same population.

Baroncelli *et al.* [3] did not include healthy controls in their study, so the association of *DEFB1* polymorphism and HIV infection in this population cannot be investigated. The authors reported an association between the −52G/G genotype and lower levels of HIV RNA in breast milk of naive HIV-positive mothers (the number of patients analyzed was not specified) but not in plasma. This finding suggests a functional role for this SNP in the modulation of hBD-1 expression and a possible effect on HIV replication, exclusively in breast milk. This hypothesis is not convincing as also the −52A/A genotype seems to associate with lower levels of HIV RNA in breast milk, moreover, the possible mechanisms related to the hypothesized *DEFB1* differential expression are not clear. In two independent studies [5,6], controversial findings about the functional effects of 5′UTR *DEFB1* SNPs on hBD-1 expression were reported, but being the peptide constitutively strongly expressed in the mucosal surfaces and epithelial cells, it is unlikely to hypothesize such a strong tissue-specific modulation. Finally, Baroncelli *et al.*'s [3] hypothesis does not consider previous findings demonstrating that hBD-2 and hBD-3 but not hBD-1 are able to inhibit in-vitro HIV-1 replication [7].

Two considerations can be made from these studies. The first concerns the population-specific variability of *DEFB1* gene; Cagliani *et al.* [8] analyzed *DEFB1* promoter region sequence variations in six distinct human populations (African–American, Asian, Australian Aborigine, European–American, South American–Indian and Yorubans) and showed a high degree of nucleotide variations as well as a substantial divergence from the assumption of evolutionary neutrality in the six populations considered. The possible explanation for the *DEFB1* gene variability restricted to the promoter region is that the functional connotation of these variations represented a selective advantage in ancient

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Table 1. Genotype and allelic frequencies of the 5′UTR *DEFB1* −52G/A, −44C/G and −20G/A SNPs in HIV-positive Brazilian children and healthy children included in the present study, in HIV-positive individuals and healthy controls reported by Braida *et al.* [1], Milanese *et al.* [2] and Baroncelli *et al.* [3].

	New study healthy controls Brazilian ($n=96$)	New study HIV+ Brazilian ($n=173$)	Milanese *et al.* [2] healthy controls Brazilian ($n=115$)	Milanese *et al.* [2] HIV+ Brazilian ($n=128$)	Braida *et al.* [1] healthy controls Italian ($n=120$)	Braida *et al.* [1] HIV+ Italian ($n=97$)	Baroncelli *et al.* [3] HIV+ Mozambican ($n=78$)	NCBI European ($n=60$)	NCBI Sub-Saharan African ($n=60$)	NCBI African–American ($n=24$)
SNP −52G/A rs1799946										
G	0.53	0.60	0.54	0.67	0.58	0.48	0.44	0.60	0.40	0.35
A	0.47	0.40	0.46	0.33	0.42	0.52	0.56	0.40	0.60	0.65
G/G	0.30	0.35	0.30	0.41	0.30	0.21	0.23	0.40	0.15	0.17
G/A	0.46	0.50	0.50	0.51	0.56	0.53	0.41	0.41	0.54	0.37
A/A	0.24	0.15	0.21	0.08	0.14	0.26	0.36	0.19	0.30	0.46
SNP −44C/G rs1800972										
C	0.87	0.88	0.86	0.93	0.78	0.90	0.94	0.75	NA	0.96
G	0.13	0.12	0.14	0.07	0.22	0.10	0.06	0.25	NA	0.04
C/C	0.77	0.76	0.73	0.85	0.58	0.84	0.87	0.61	NA	0.92
C/G	0.20	0.23	0.25	0.15	0.39	0.14	0.13	0.28	NA	0.08
G/G	0.03	0.005	0.02	0	0.03	0.02	0	0.11	NA	0
SNP −20G/A rs11362										
G	0.64	0.56	0.63	0.48	0.62	0.62	NA	0.67	0.68	0.73
A	0.36	0.43	0.37	0.52	0.38	0.38	NA	0.33	0.32	0.27
G/G	0.39	0.33*	0.36	0.12*	0.36	0.37	NA	0.48	0.45	0.54
G/A	0.50	0.47*	0.53	0.73*	0.52	0.49	NA	0.37	0.45	0.38
A/A	0.11	0.20*	0.10	0.15*	0.12	0.14	NA	0.15	0.10	0.08

NCBI 5′UTR *DEFB1* genotype and allele frequencies of European, Sub-Saharan African and African–American populations are also reported. HIV+, HIV-positive patients; NA, not available; NCBI, National Center for Biotechnology Information; SNP, single nucleotide polymorphism.
*HIV-positive patients −20G/A genotype distribution, P is less than 1×10^{-05} in the present study vs. Milanese *et al.* [2].
The present study HIV-positive patients vs. present study healthy controls, P is greater than 0.05 for all SNPs; for HIV-positive patients vs. healthy controls in Milanese *et al.* [2] and Braida *et al.* [1] see correspondent references.

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populations and fixed their frequencies with a heterozygous advantage mechanism.

As recently suggested, population stratification should be tested by using a panel of 25 SNPs, described by Barreiro *et al.* [9], in order to correctly identify a population's ethnic origin when dealing with *DEFB1* promoter polymorphisms.

The second consideration concerns the controversial findings reported by different authors on *DEFB1* mRNA expression in various tissues or cell lines [5,6,10]. The best strategy to analyze the potential functional role of *DEFB1* promoter SNPs in the modulation of hBD-1 expression may be the quantitative evaluation of hBD-1 peptide, in patients with known *DEFB1* genotype, by using a specific anti-hBD-1 antibody.

In conclusion, we suggest that when looking for association with HIV infection risk, the 5′UTR *DEFB1* polymorphisms should cautiously be considered, being that their frequencies are so variable between populations and, as we demonstrated, within the same population. Their possible association with a detrimental effect on HIV replication in milk of HIV-positive mothers should be verified on a larger number of women and functional data will be required to support the hypothesis of a differential tissue expression.

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L.S. redacted the manuscript and performed statistical analysis; L.B. performed *DEFB1* genotyping; R.G. performed samples recruitment and DNA extraction; S.C. performed the study design and redacted the manuscript.

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References

1. Braida L, Boniotto M, Pontillo A, Tovo PA, Amoroso A, Crovella S. **A single-nucleotide polymorphism in the human beta-defensin 1 gene is associated with HIV-1 infection in Italian children.** *AIDS* 2004; **18**:1598–1600.
2. Milanese M, Segat L, Pontillo A, Arraes LC, de Lima Filho JL, Crovella S. **DEFB1 gene polymorphisms and increased risk for HIV-1 infection in Brazilian children.** *AIDS* 2006; **20**:1673–1675.
3. Baroncelli S, Ricci E, Andreotti M, Guidotti G, Germano P, Marazzi MC, *et al*. **Single-nucleotide polymorphisms in human beta-defensin-1 gene in Mozambican HIV-1-infected women and correlation with virologic parameters.** *AIDS* 2008; **22**:1515–1517.
4. Alves-Silva J, da Silva Santos M, Guimaraes PE, Ferreira AC, Bandelt HJ, Pena SD, *et al*. **The ancestry of Brazilian mtDNA lineages.** *Am J Hum Genet* 2000; **67**:444–461.
5. Sun CQ, Arnold R, Fernandez-Golarz C, Parrish AB, Almekinder T, He J, *et al*. **Human beta-defensin-1, a potential chromosome 8p tumor suppressor: control of transcription and induction of apoptosis in renal cell carcinoma.** *Cancer Res* 2006; **66**:8542–8549.
6. Milanese M, Segat L, Crovella S. **Transcriptional effect of DEFB1 gene 5′ untranslated region polymorphisms.** *Cancer Res* 2007; **67**:5997.
7. Quiñones-Mateu ME, Lederman MM, Feng Z, Chakraborty B, Weber J, Rangel HR, *et al*. **Human epithelial beta-defensins 2 and 3 inhibit HIV-1 replication.** *AIDS* 2003; **17**:F39–F48.
8. Cagliani R, Fumagalli M, Riva S, Pozzoli U, Comi GP, Menozzi G, *et al*. **The signature of long-standing balancing selection at the human defensin beta-1 promoter.** *Genome Biol* 2008; **9**:R143.
9. Barreiro LB, Neyrolles O, Babb CL, Tailleux L, Quach H, McElreavey K, *et al*. **Promoter variation in the DC-SIGN-encoding gene CD209 is associated with tuberculosis.** *PLoS Med* 2006; **3**:e20.
10. Zapata W, Rodriguez B, Weber J, Estrada H, Quiñones-Mateu ME, Zimermman PA, *et al*. **Increased levels of human beta-defensins mRNA in sexually HIV-1 exposed but uninfected individuals.** *Curr HIV Res* 2008; **6**:531–538.

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Response to Segat *et al.* 'Are *DEFB1* gene polymorphisms associated with HIV-1 infection and virus replication?'

In a recent letter, Segat *et al.* [1] reported new data on the frequencies of single nucleotide polymorphisms (SNPs) of the human β defensin-1 (*DEFB1*) gene in a population of Brazilian HIV-1-infected children and compared these data with the results of other studies, including those previously performed on HIV-1-infected children by the same research group.

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This new study did not confirm the significant association between the −52GG and −20AA genotypes of the *DEFB1* gene and HIV-1 infection, found in a previous study performed on Brazilian HIV-1-infected and uninfected children [2]. Furthermore, these new data also differed from those previously reported on Italian HIV-1-infected and healthy children, in whom the −44C/G SNP was found to influence HIV-1 infection [3]. In light of these findings, the authors conclude that the role of *DEFB1* gene polymorphisms should be redefined. Considering the variability found in different and even the same populations, we agree that more caution should be taken regarding this issue. However, although genetic differences between different populations could partially explain the different results, it should be taken into account that inconsistent results may be generated by the small size of the studied population and by the lack of relevant controls.

It appears more difficult to extend the concerns of Segat *et al.* [1] about the role of *DEFB1* in HIV-1 infection to our study [4], which analyzed the frequencies of *DEFB1* gene polymorphisms in HIV-1-infected Mozambican women and the association of these frequencies with viral load. In antiretroviral-untreated women ($n = 38$), we found a significant association between the −52GG genotype and a lower viral load in breast milk. Segat *et al.* [1] state that our results are not convincing as even women with the −52AA genotype had lower viral load in breast milk than those with the −52GA genotype. This is true, but the difference was statistically significant only for the −52GG genotype.

Different from the authors' assertions, our data are consistent with the finding that the −52AA and −52GA genotypes are correlated with reduced expression of *DEFB1* [5,6]. Contrary to what Segat *et al.* [1] stated regarding the possible different expression of *DEFB1* in different districts (blood and mammary gland tissue), our results are supported by other authors who found higher concentrations of *DEFB1* in breast milk than in other mucosal surfaces, [7,8], with a marked increase in *DEFB1* expression during lactation [8]. Moreover, the relative incapacity of *DEFB1* to inhibit in-vitro HIV-1 infection ([9], but not fully confirmed by other authors [10]), is not in contrast with our results. Indeed, in our study, we reported a lower HIV-1 viral load in the breast milk of women with the −52GG genotype, but we did not describe a direct effect of *DEFB1* on HIV-1 replication. It is well known that inflammation, such as mastitis or local infection, can favor HIV-1 replication in mammary tissues [11,12]; thus, the antimicrobial function of β-defensins could exert an indirect effect on HIV-1 replication.

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References

1. Segat L, Brandao LAC, Guimaraes RL, Crovella S. **Are DEFB1 gene polymorphisms associated with HIV infection and viral replication?** *AIDS* (in press).
2. Milanese M, Segat L, Pontillo A, Arraes LC, de Lima Filho JL, Crovella S. **DEFB1 gene polymorphisms and increased risk of HIV-1 infection in Brazilian children.** *AIDS* 2006; **20**:1673–1675.
3. Braida L, Boniotto M, Pontillo A, Tovo PA, Amoroso A, Crovella S. **A single-nucleotide polymorphism in the human beta-defensin 1 gene is associated with HIV-1 infection in Italian children.** *AIDS* 2004; **18**:1598–1600.
4. Baroncelli S, Ricci E, Andreotti M, Guidotti G, Germano P, Marazzi MC, *et al.* **Single-nucleotide polymorphisms in human beta-defensin-1 gene in Mozambican HIV-1-infected women and correlation with virologic parameters.** *AIDS* 2008; **22**: 1515–1517.
5. Milanese M, Segat L, Crovella S. **Transcriptional effect of DEFB1 gene 5′ untranslated region polymorphisms.** *Cancer Res* 2007; **67**:5997.
6. Kocsis AK, Kiss ZF, Tiszlavicz L, Tiszlavicz Z, Mandi Y. **Potential role of human beta-defensin 1 in Helicobacter pylori-induced gastritis.** *Scand J Gastroenterol* 2008; **8**:1–7.
7. Tunzi CR, Harper PA, Bar-Oz B, Valore EV, Semple JL, Watson-MacDonell J, *et al.* **Beta-defensin expression in human mammary gland epithelia.** *Pediatr Res* 2000; **48**:30–35.
8. Jia HP, Starner T, Ackermann M, Kirby P, Tack BF, McCray PB Jr. **Abundant human beta-defensin-1 expression in milk and mammary gland epithelium.** *J Pediatr* 2001; **138**:109–112.
9. Quiñones-Mateu ME, Lederman MM, Feng Z, Chakraborty B, Weber J, Rangel HR, *et al.* **Human epithelial beta-defensins 2 and 3 inhibit HIV-1 replication.** *AIDS* 2003; **17**:F39–F48.
10. Sun L, Finnegan CM, Kisk-Catalone T, Blumenthal R, Garzino-Demo P, La Terra Maggiore GM, *et al.* **Human beta-defensins supress human immunodeficiency virus infection: potential role in mucosal protection.** *J Virol* 2005; **22**:14318–14329.
11. Phiri W, Kasonka L, Collin S, Makasa M, Sinkala M, Chintu C, *et al.* **Factors influencing breast milk HIV RNA viral load among Zambian women.** *AIDS Res Hum Retroviruses* 2006; **22**:607–614.
12. Kantarci S, Koulinska IN, Aboud S, Fawzi WW, Villamor E. **Subclinical mastitis, cell-associated HIV-1 shedding in breast milk, and breast-feeding transmission of HIV-1.** *J Acquir Immune Defic Syndr* 2007; **46**:651–654.

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