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*Original Article*

# Prevalence of common vitamin D receptor gene polymorphisms in HIV-infected and uninfected South Africans

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**Abstract:** *Background:* Host genetic factors may a play role in susceptibility to infection. Vitamin-D is an immunomodulator that may play a role in HIV infection. Vitamin-D action is mediated by the vitamin-D receptor. We establish prevalence of ApaI, BsmI, FokI and TaqI polymorphisms (VDRPs) amongst a black southern African HIV+ve population and investigate polymorphic differences between HIV+ve and -ve people. *Methods:* Seventy-nine sex and age-group matched HIV+ve patients of African origin initiating antiretroviral therapy (ART) and 79 HIV-ve participants, also of African origin, were recruited from a public sector HIV testing and treatment clinic and investigated for the 4 polymorphisms. The genotype frequencies were compared, odds ratios and 95% confidence intervals of the association of HIV status and each genotype were calculated. Both dominant, co-dominant, recessive and allele models were tested. *Results:* We found no evidence of difference in distribution and association between HIV infection and the genotypes of the BsmI, FokI and TaqI VDR polymorphisms. The genotype distributions were consistent with Hardy-Weinberg equilibrium for these genotypes. The ApaI genotype showed differences in distribution by HIV status in the dominant and co-dominant models. However this finding is cautiously stated as the ApaI genotype violated the Hardy-Weinberg equilibrium and frequency of the minor variant was unexpectedly low in this population. *Conclusion:* We do not show convincing differences in distribution of the VDR genotypes among HIV+ve and HIV-ve black southern African persons. Future studies need to be replicated in larger study populations as understanding polymorphic differences and similarities may offer insights into the different susceptibility and progression of HIV in southern African populations.

**Keywords:** Vitamin D, vitamin D receptor polymorphisms, HIV infection, Southern Africa

## Background

The potent immunomodulatory functions of 1-25-dihydroxyvitamin D3 (1,25(OH)2D), the active metabolite of vitamin D are clearly established [1]. A growing body of evidence suggests an association of vitamin D deficiency with significant morbidity, increased risk of cancers, autoimmune diseases and possible susceptibility to infectious diseases [2-9]. 1,25(OH)2D plays an important role in initiating autophagy, a vital process in the destruction of microorganisms. Several studies suggest that 1,25 (OH)2D triggered autophagy is implicated in combating a wide range of bacterial or viral infectious agents including *Staphylococcus aureus*, *Listeria monocytogenes*, *Chlamydia trachomitis*, CMV, *Herpes simplex*, Dengue, respiratory syncitial virus and others [10-12]. Emerging evidence suggests that HIV may also be under the control of autophagy [13, 14]. In addition, laboratory studies have identified several mechanisms by which vitamin D could slow HIV disease progression and, as clinical and genetic evidence continues to accumulate on the immune functions of vitamin D, it is now postulated that vitamin D plays a crucial role in modulating HIV infection [15]. Laboratory models of HIV infection have shown that pre-treatment of human monocytes and macrophages with 1,25(OH)2D prevents HIV infection in certain cell-lines [16], while increasing HIV replication in others [17]. In addition cathelicidin, the antimicrobial peptide, regulated in part by vita-

min D, has been shown to directly inhibit replication of HIV [18].

The role of Vitamin D in HIV infection has further been supported by studies implicating polymorphisms in the VDR gene in infectious disease and HIV infection susceptibility and progression [19-22]. Several single-nucleotide polymorphisms (SNPs) have been identified in the VDR gene. The ApaI, BsmI and TaqI polymorphisms occur in the 3'-UTR region of the gene and the FokI polymorphism is found in the translation initiation codon. VDR polymorphisms have been associated with susceptibility to infection by a number of bacterial pathogens and viruses, including *Mycobacterium tuberculosis*, *Mycobacterium leprae* and Hepatitis B virus [22-29]. In a case-control study investigating VDR polymorphisms FokI, BsmI, ApaI, and TaqI and tuberculosis susceptibility among the Venda in South Africa, the VDR polymorphisms were not associated with tuberculosis, but the haplotype F-b-A-T significantly protected from tuberculosis infection [25]. In a West African study, variation in the VDR gene was shown to confer resistance to tuberculosis and persistent Hepatitis B infection [24]. However, studies examining the relationship between these single nucleotide polymorphisms and HIV infection susceptibility are sparse. A study conducted in Spain among intravenous drug users suggested that HIV seropositive patients heterozygous for the FokI polymorphism could be considered prone to a faster progression to AIDS, and a further study among the same population suggested that the BsmI polymorphism is not involved in initial susceptibility to infection with HIV, but that homozygosity could be considered a risk factor for less favourable progression of HIV disease [20, 21].

The current study was undertaken to establish the prevalence of 4 common SNPs (ApaI, BsmI, FokI and TaqI) of the Vitamin D receptor in a southern African HIV infected population and whether the prevalence differed in the sample of age and sex matched HIV negative people from the same population.

## Methods

### *Patients and controls*

The Themba Lethu Clinic (TLC) in Johannesburg, South Africa, was started in 2004 as a public sector HIV treatment site and has been described elsewhere [30]. Cases were selected from four hundred and four HIV-infected (HIV+ve) black patients of African origin aged >18 years, eligible to begin antiretroviral therapy who were recruited from the clinic on the day they began antiretroviral therapy between November 2008 and March 2009. One hundred consecutive walk-in patients aged >18 years, also black and of African origin, who tested HIV negative (HIV-ve) and agreed to participate in the study, were also recruited from the same clinic as potential controls. Matching by sex and 5-year age bands, seventy-nine of the HIV+ve patients were matched to seventy-nine HIV-ve controls. Cases and controls were investigated for the same polymorphisms.

### *Ethics statement*

This analysis was nested within ongoing cohort studies of routine ART outcomes at the Themba Lethu Clinic, Helen Joseph Hospital in Johannesburg. Permission to use patient data from the Themba Lethu Clinic was granted by the superintendent of Helen Joseph Hospital. All participants gave written informed consent to have blood drawn for DNA analysis. The study and study procedures were approved by the Human Research Ethics Committee of the University of the Witwatersrand (M070604). Individual patient consent for analysis of treatment outcomes was not needed, consistent with the South African Medical Research Council's Guidelines on Ethics for Medical Research and the Declaration of Helsinki. As this was a retrospective analysis of routine clinical service records, no additional data collection or procedures were undertaken from or on patients beyond DNA analysis. All patient information was entered into the database using coded identification numbers, and no information that could reveal patient identity was available in the analytic datasets.

### *Genotyping*

Genomic DNA was extracted from whole blood using standard methods. DNA from each person was analysed for the vitamin D receptor ApaI (rs7975232), BsmI (rs1544410), FokI (rs2228570) and TaqI (rs731236) SNPs using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) according to the manufacturer's instructions (Anatech™, Johannesburg, South Africa). Primers used

**Table 1.** Baseline characteristics of the HIV infected patients and healthy controls

| Characteristics | HIV positive | HIV negative |
|---|---|---|
| Total, n | 79 | 79 |
| Sex, n (%) | | |
| Male | 44 (55.7) | 44 (55.7) |
| Female | 35 (44.3) | 35 (44.3) |
| Age (years), median (IQR) | 33.8 (25.8-40.9) | 34 (28-42) |
| CD4 cell count (cells/ml), median (IQR) | 75 (40-145) | |
| BMI (kg/m$^2$), median (IQR) | 21.7 (17.9-23.5) | |
| Haemoglobin (g/dl), median (IQR) | 11.4 (10.2-12.9) | |
| Tuberculosis diagnosis, n (%) | | |
| No | 61 (77.2) | |
| Yes | 18 (22.8) | |
| WHO clinical stage, n (%) | | |
| I/II | 32 (41.6) | |
| III/IV | 45 (58.4) | |

were those designed by Israni and others [31]. Restriction digestion of the PCR product was performed according to the manufacturer's instructions and the digested products were analyzed by electrophoresis in a 2% agarose gel incorporating GelRed™ (Anatech, Johannesburg, South Africa). The presence and absence of a restriction site were assigned a lowercase and uppercase letter, respectively (a and A for ApaI, b and B for BsmI, f and F for FokI and t and T for TaqI).

*Statistical analysis*

Descriptive statistics were used to summarize the baseline characteristics of cases and controls. The genotype and allelic distribution between HIV+ve patients and HIV-ve controls were compared by the Pearson's chi-square or Fishers exact test and the chi-square test for trend (p-trend). We tested both the dominant, recessive, over-dominant, co-dominant and the allele models of the genotypes. The three kinds of genotypes were transformed into two variables. For example, the dominant model compares BB versus Bb+bb, and the recessive model compares BB+Bb versus bb. An over-dominant model assumes the heterozygote has the strongest impact and compares BB+bb versus Bb. On the other hand, co-dominant models hypothesize that BB, Bb, and bb are associated with the lowest, the intermediate, and the highest risk, respectively, or they are associated with the highest, the intermediate, and the lowest risk, respectively [32, 33]. The allelic model evaluates the impact of individual alleles on the disease e.g. B vs. b. The odds ratio (OR) and 95% confidence intervals (95% CI) of the association between the polymorphisms with HIV status were also determined using logistic regression. Multiple comparisons were corrected by the Bonferroni method (adjusted $p$-value = 0.05/6 = 0.0083). The Hardy Weinberg equilibrium was tested using the goodness-of-fit chi-square. Data analyses were performed using Stata v13 (Stata Corp, College Station, TX, USA).

## Results

Seventy-nine cases were matched to seventy-nine controls (1:1) on sex and 5-year age bands. **Table 1** shows the baseline characteristics of cases and controls. The controls came from the same population as cases and attended the same clinic for HIV testing, only HIV status, race, sex and age were collected. There were 44 males (55.7%) and 35 females (44.3%) in each group. Median age among the HIV infected patients was 33.8 years vs. 34 years for the uninfected persons.

The genotype frequencies for the BsmI, FokI and TaqI in both HIV+ve patients and healthy controls did not violate the Hardy-Weinberg equilibrium (all $p$-values >0.05). The distribution of the BsmI, FokI and TaqI genotypes among HIV infected patients (cases) and the healthy controls was largely similar. The majority of the HIV infected cases and healthy participants carried the BsmI-bb genotype (57.7% and 49.4% respectively), whereas the BsmI-BB genotype was in the minority of cases and controls (5.1% and 5.1% respectively). For the FokI genotype, the ff variant was in the minority of the participants (1.3% in cases and 1.3% in controls) whereas the FF variant was in the majority of the cases (63.6%) and controls (68.4%). The tt variant of the TaqI genotype also had lowest frequency among cases (3.9%) and controls (2.5%) compared to the TT variant (64.1% in cases and 80% in controls). The frequency distributions are shown in **Table 2**. Logistic regression analysis did not reveal any association between the genotype variants and HIV infec-

**Table 2.** Genotype and allele frequencies of vitamin D receptor gene polymorphisms in HIV infected patients and healthy controls in Johannesburg, South Africa

| rs no. | Genotype | HIV positive n (%) | HIV negative n (%) | Odds Ratio (95 % CI) | *p*-value | p-trend |
|---|---|---|---|---|---|---|
| rs7975232 (ApaI) | AA | 27 (35.5) | 46 (58.2) | 1.00 (Reference) | | |
| | Aa | 44 (57.9) | 32 (40.5) | 2.34 (1.21-4.52) | 0.011 | |
| | aa | 5 (6.6) | 1 (1.3) | 8.52 (0.95-76.80) | 0.056 | 0.003 |
| | Aa+AA vs. aa | | | 0.18 (0.02-1.60) | 0.124 | |
| | AA+aa vs. Aa | | | 0.50 (0.26-0.94) | 0.031 | |
| | Aa+aa vs. AA | | | 2.53 (1.32-4.84) | 0.005 | |
| | A vs. a allele | | | 0.50 (0.27-0.94) | 0.029 | |
| rs1544410 (BsmI) | BB | 4 (5.1) | 4 (5.1) | 1.00 (Reference) | | |
| | Bb | 29 (37.2) | 36 (45.6) | 0.81 (0.19-3.50) | 0.773 | |
| | bb | 45 (57.7) | 39 (49.4) | 1.15 (0.27-4.93) | 0.847 | 0.334 |
| | Bb+BB vs. bb | | | 0.72 (0.38-1.34) | 0.296 | |
| | BB+bb vs. Bb | | | 1.41 (0.75-2.68) | 0.287 | |
| | Bb+bb vs. BB | | | 0.99 (0.24-4.09) | 0.985 | |
| | B vs. b allele | | | 1.23 (0.65-2.32) | 0.519 | |
| rs2228570 (FokI) | FF | 49 (63.6) | 54 (68.4) | 1.00 (Reference) | | |
| | Ff | 27 (35.1) | 24 (30.4) | 1.24 (0.63-2.43) | 0.531 | |
| | ff | 1 (1.3) | 1 (1.3) | 1.10 (0.07-18.10) | 0.946 | 0.541 |
| | Ff+FF vs. ff | | | 0.97 (0.06-15.90) | 0.985 | |
| | FF+ff vs. Ff | | | 0.81 (0.41-1.58) | 0.533 | |
| | Ff+ff vs. FF | | | 1.23 (0.64-2.40) | 0.534 | |
| | F vs. f allele | | | 0.81 (0.39-1.69) | 0.577 | |
| rs731236 (TaqI) | TT | 50 (64.1) | 60 (80.0) | 1.00 (Reference) | | |
| | Tt | 25 (32.05) | 17 (21.5) | 1.76 (0.86-3.63) | 0.123 | |
| | tt | 3 (3.9) | 2 (2.5) | 1.80 (0.29-11.20) | 0.529 | 0.108 |
| | Tt+TT vs. tt | | | 0.65 (0.11-4.00) | 0.641 | |
| | TT+tt vs. Tt | | | 0.58 (0.28-1.19) | 0.138 | |
| | Tt+tt vs. TT | | | 1.77 (0.88-3.54) | 0.107 | |
| | T vs. t allele | | | 0.60 (0.28-1.28) | 0.182 | |

Bonferroni adjusted *p*-value = 0.05/6 = 0.0083. Hardy-Weinberg Equilibrium *P*-values: Cases (ApaI = 0.021, BsmI = 0.808, FokI = 0.197 and TaqI = 0.955) and Controls (ApaI = 0.077, BsmI = 0.234, FokI = 0.351 and TaqI = 0.555).

tion status. The lack of association was observed in both dominant, recessive, co-dominant and the allele models. This lack of association was maintained after the Bonferroni correction for multiple testing (adjusted *p*-value = 0.0083). This is shown in **Table 2**.

The ApaI genotype frequency in cases violated the Hardy-Weinberg equilibrium (p = 0.021), whereas the distribution in controls approached statistical significance (p = 0.077). For the ApaI genotype, the frequency of the aa variant was minor across all participants regardless of HIV status, 6.6% versus 1.3%. The Aa variant had the majority frequency in HIV infected participants (57.9%), whereas the AA had the major frequency among the controls (58.2%). After the Bonferroni correction for multiple testing (adjusted *p*-value = 0.0083), association of HIV status with ApaI genotype was maintained for the dominant and co-dominant models (AA vs. Aa+aa: OR = 2.53, 95% CI 1.32-4.84, p = 0.005 and p-trend = 0.003 respectively).

## Discussion

Although a few studies have previously described the prevalence of the VDR gene poly-

morphisms in African persons, the distribution of these 4 common polymorphisms in the VDR gene among the black HIV-infected population in sub-Saharan Africa has not been described before. This study reports on the distribution of the common VDR genotypes among HIV+ve and HIV-ve participants in a Southern African population. The distribution was similar with the BsmI, FokI and TaqI polymorphisms, suggesting no association with HIV infection status. There was an apparent difference in the distribution of the ApaI polymorphisms between HIV+ve and HIV-ve participants. However, the ApaI genotype frequency violated the Hardy-Weinberg equilibrium making this finding difficult to interpret.

To date, we are unaware of any studies that have compared these VDR genotypes in African HIV+ve and HIV-ve populations. Thus far, among HIV-infected persons, the VDR gene polymorphisms have been analysed mostly in Caucasian populations. The genotype frequencies we present among the HIV-uninfected controls are in agreement with genotype frequencies reported previously among African persons in South and West Africa whereas the frequencies for the ApaI genotype was unexpectedly low in HIV-ve compared to those reported by Bornmen et al. in 634 healthy West African controls [24, 25]. The genotype frequencies we observe are however different to those seen in Caucasian populations. As previous studies have demonstrated that genotype frequencies of these factors differ between populations, they are also more likely to play different roles in different populations.

When we compared the African HIV+ve population to an HIV-ve population, we observed some differences in the ApaI polymorphism. This finding should be interpreted in light of the limitation that the Hardy-Weinberg equilibrium was violated with the ApaI genotype distribution. Also deviation from Hardy-Weinberg equilibrium in this study may have also been due to our small sample size. While we restricted the study population to Black southern Africans attending an urban South African clinic, subtle difference of population admixture cannot be excluded and may limit our observations and inferences.

The lack of association between HIV status and VDR SNPs in this study has been demonstrated in other populations. In a study among Caucasian HIV infected and uninfected intravenous drug users, no association of the FokI polymorphism with HIV status was found [21]. Also, in another study, there were no significant differences in the BsmI-VDR genotype frequencies between HIV-ve persons and HIV-positive intravenous drug users suggesting that this polymorphism of the VDR locus did not affect initial HIV infection [19]. Haplotype analysis in this situation is of interest. Algarasu and coworkers [22] showed that, in a south Indian population, the b-A-T haplotype may be protective against HIV infection.

In conclusion, we have not demonstrated any convincing differences in VDR genotypes between HIV+ve and HIV-ve black Africans. Disease susceptibility is a complex interaction between host, agent and environment. Investigating genotype differences between HIV+infected and uninfected populations especially in the VDR complex, a potent immunomodulator, might offer some insight into understanding the susceptibility to HIV infection in southern African populations. Further studies of larger samples, including haplotype analysis, are required in order to fully elucidate the functional significance of VDR polymorphisms in the susceptibility to HIV infection.

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## Disclosure of conflict of interest

None.

## Authors' contribution

The study was conceived and designed by LM, ST and PM. Laboratory work was conducted by LM. Statistical analysis was conducted by ST and TC. All authors contributed to the writing of the manuscript and read and approved the final version.

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