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Risky sexual behavior and its associated factors among high school and preparatory night students in Awi zone, northwest, Ethiopia

Belayneh Fentahun Shibesh

Department of General Medicine, Bangalore Medical College & Research, Ethiopia

Abstract

Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). It spreads from person to person mainly by sexual route (most common), parenteral (blood transfusion, needle sharing in drug use, needle stick injury etc).1 According to India HIV Estimation 2017 report, 2.1 million people were living with HIV. National adult (15–49 years) HIV prevalence in India is estimated to be 0.22% (0.16% – 0.30%) in 2017. 0.25% (0.18-0.34) among males and at 0.19% (0.14-0.25) among females. The adult HIV prevalence at national level has continued its steady decline from an estimated peak of 0.38% in 2001-03 through 0.34% in 2007 0.28% in 2012 and 0.26% in 2015 to 0.22% in 2017. AIDS related deaths has declined by almost 71%. 2 India is the third largest country with HIV/AIDS patients.

Keywords: Nucleoside reverse transcriptase inhibitors • Lamivudine • Emtricitabine • Mean corpuscular volume

Introduction

It is known that thymidine analogues of the nucleoside reverse transcriptase inhibitor (NRTI) drug category, particularly stavudine and zidovudine, caused an increase in the mean corpuscular volume (MCV) of erythrocytes, and this can be sufficient to cause macrocytosis [1]. Newer NRTIs, often of the non-thymidine class, such as lamivudine, are now more frequently used as the backbone for antiretroviral drug regimens. The evidence regarding the effect of these NRTIs on MCV is less well established. Three prior studies have suggested an increase in MCV with lamivudine [2-4], whilst another study showed no significant effect [5]. These studies have examined small numbers of patients only and results are difficult to interpret as patients were frequently co-prescribed other NRTIs known to affect the MCV.

Lamivudine is being increasingly used in dual antiretroviral therapy as a result of recent studies [6]. It is therefore clinically important to understand the effect of lamivudine on MCV, as this will guide investigations in patients found to have macrocytosis while taking lamivudine.

Aim

The aim of this study was to assess the mean corpuscular volume of erythrocytes in patients taking lamivudine, when the effects of other NRTIs and other biochemical or haematological factors affecting the MCV were excluded.

***Address for Correspondence:** Clemency Nye, Core Medical Trainee, North Bristol NHS Trust, Bristol, England, UK, Tel: +44 117 950 5050; E-mail: clemency.nye@gmail.com*

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Research Methodology

Using anonymized data from the electronic records of patients at a single urban UK centre, we selected patients who had been prescribed lamivudine as part of anti-retroviral therapy between 2000 and 2019, and analysed their most recent full blood count whilst taking lamivudine. We then compared these results with those of a randomly selected comparison group of patients who were not taking lamivudine or any other NRTI previously known to affect MCV.

Patients were excluded from the lamivudine group if they had been prescribed azidothymidine, emtricitabine, zidovudine or stavudine concurrently. Patients who had taken lamivudine for less than 3 months, or who had not had a full blood count (FBC) after more than 3 months on lamivudine, were also excluded as it is likely that the greatest impact on MCV occurs after 3 months, reflecting the lifespan of the erythrocyte [7]. Patients with an abnormally high or low MCV were excluded if there were other biochemical or haematological factors which could alter the MCV. Patients with a low MCV (< 83 g/dL) were excluded if they had evidence of iron deficiency within the last year, or were known to have a haemoglobinopathy. Patients with an abnormally high MCV (> 100 g/dL) were excluded if they had evidence of B12 or folate deficiency within the last year, active hypothyroidism with a raised TSH within the last year, or were known to drink alcohol to excess as recorded in HIV record.

A comparison group was created from patients randomly selected from the electronic record. The same exclusions as above were applied. In addition, patients who were currently taking lamivudine, azidothymidine, zidovudine or stavudine or had stopped taking these medications less than 12 months previously were excluded. Patients taking emtricitabine were included, as there is little evidence that this NRTI affects the MCV (1) – this group was later examined further.

Results

In total, 579 patients had been prescribed lamivudine between 2000

and 2019. Eighty-eight patients were excluded due to either incomplete data regarding the dates of lamivudine therapy, total time on lamivudine of less than 3 months, or lack of full blood count after more than 3 months on lamivudine. Twenty of 27 patients with abnormally low MCV (<83 g/dL) were excluded – 7 iron deficiency and 13 haemoglobinopathies. 15 of 64 patients with abnormally high MCV were excluded – 4 folate deficiency, 1 active hypothyroidism and 10 alcohol excess. After exclusions, 456 patients remained in the lamivudine group. After similar exclusions, 483 remained in the comparison group.

Demographics of the two groups were compared, including age, sex, ethnicity, and HIV risk group, and there were no significant differences between the groups (Table 1).

The majority of the comparison group (87.0%) were taking combination therapy containing emtricitabine. We therefore further subdivided the complete comparison group (Group 2) into patients taking emtricitabine (Group 3) and patients not taking emtricitabine (Group 4). 38% of patients in group 4 were prescribed either tenofovir or abacavir and the remainder were not taking any NRTI.

The mean MCV in the lamivudine group (group 1) was 94.1 and in group 2 were 91.6. Using the independent t-test, there was a statistically significant difference between the MCV of the lamivudine group, and each of the three other groups (Table 2).

It is notable that there is a greater difference in the mean MCV between the lamivudine group and group 4 compared to that between the lamivudine group and group 3. There was also a statistically significant difference in the mean MCV of group 3 and group 4 (difference -2.04 with p-value 0.002). This suggests that emtricitabine, which is structurally similar to lamivudine, may also have an effect on MCV, albeit it to a lesser degree than lamivudine.

There was no difference in mean MCV when either group data was subdivided by age groups, ethnicity or sex. Lamivudine drug levels are not routinely measured in clinical practice, but there was no difference in mean MCV between patients prescribed different doses of lamivudine (either 150 mg or 300 mg), and no correlation between patient weight and MCV, including when subdivided by gender. In the control group, there was no difference between mean MCV in patients who had or had not previously taken lamivudine or other NRTIs affecting MCV.

Forty-nine patients, or 10.7%, of the lamivudine group had an MCV of greater than 100 g/dL and therefore were in the macrocytic range. The odds ratio for macrocytosis was 3.3 for group 1 compared to group 2. There were no differences apparent in the demographics of the macrocytic patients compared to the lamivudine group as a whole, including in weight, duration on lamivudine, or dose of lamivudine.

Discussion

This study provides evidence to suggest that lamivudine increases the mean corpuscular volume of erythrocytes, and that this is sufficient to cause macrocytosis in 10% of patients. It also indicates that emtricitabine may have a similar effect on MCV, although the increase in MCV is less marked than that with lamivudine.

There are no recent studies on lamivudine and MCV. Prior study results are often difficult to interpret due to concurrent use of other NRTIs, small sample sizes and lack of exclusion of other factors affecting the MCV, such as nutritional deficiencies, haemoglobinopathies, hypothyroidism or excess alcohol use.

In 2002, Steele assessed the degree of rise in MCV above baseline from initiation of antiretroviral therapyand found a significant rise in the 8 patients studied who had been prescribed lamivudine without azidothymydine or stavudine [3]. Diop in 2006 assessed MCV as part of a study assessing the reliability of HbA1c in patient's prescribed anti-retroviral therapy, and found that macrocytosis was associated with lamivudine, although a significant proportion of these patients were also prescribed other NRTIs affecting the MCV [4]. Kwachorenporn conducted a retrospective study in 2007 with a population of 60 patients and showed that lamivudine use was associated with increased likelihood of macrocytosis [2]. However, the numbers in this study are small, with only 21 patients prescribed lamivudine, and it is unclear how many of these were macrocytic.

Petersen in 2005 followed the MCV in patients during treatment with different anti-retroviral medications and found no clear evidence of lamivudine causing increase in MCV, although it did cause a small but nonsignificant increase when added to zidovudine or stavudine monotherapy. However, 114 of 139 patients on lamivudine were again concurrently prescribed zidovudine or stavudine, which are both known to cause macrocytosis.

A key problem in the majority of studies has been isolating the effect of lamivudine from that of other NRTIs concurrently prescribed. This study has

Table 1: demographics.

	Lamivudine group (group 1) (total 456)	Total comparison group (group 2) (total 483)
	N_(%)	N_(%)
Sex at birth:		
Male	319 (70)	370 (77)
Female	137 (30)	113 (23)
Age:		
18-29	38 (8)	17 (4)
30-44	141 (31)	187 (39)
45-59	206 (45)	212 (43)
60-74	61 (13)	58 (12)
>75	10 (2)	9 (2)
Ethnicity:		
White British	253 (56)	273 (57)
Black	113 (25)	114 (24)
Other	90 (20)	96 (20)
Risk group:		
Heterosexual	206 (45)	221 (46)
Men who have sex with men	218 (48)	231 (48)
Other	32 (7)	31 (6)
Duration of time on treatment		
Mean (months)	34	27
Median (months)	24	16
Duration on treatment before MCV		
Mean (months)	31	21
Median (months)	20	10

Table 2: MCV and macrocytosis by patient group.

	Group 1 – patients taking lamivudine (456)	Group 2 – all patients not taking lamivudine (483)	Group 3 – patients taking emtricitabine (420)	Group 4 – patients not prescribed any NRTI known to affect MCV (63)
Mean MCV	94.1 (sd 5.29)	91.6 (sd 4.98) p<0.0001 vs Group 1	91.8 (sd 4.87) p<0.0001 vs Group 1	89.8 (sd 5.26) p<0.0001 vs Group 1
Number MCV > 100	49	17	17	0
Odds ratio for macrocytosis compared to group 1	-	3.30 95% CI 1.9 to 5.9 p-value < 0.0001**	2.85 95% CI 1.6 to 5.0 p-value 0.0003**	15.43 95% CI 0.94 to 253.2 p-value 0.05

attempted to address this problem by creating a large population of patients taking lamivudine without other conflicting NRTIs, now that this is a common prescribing practice in antiretroviral therapy. It remains difficult to create the ideal comparison group of patients who are not taking any NRTIs with a possible impact on MCV, although we have attempted to address a potential effect of emtricitabine by dividing the control group into patients by emtricitabine use. There remain patients in all groups taking tenofovir or abacavir, although an effect on MCV has not been attributed to either of these NRTIs [1].

There are a number of strengths to this study. The dataset is large in both groups, although the subgroup of patients not taking any NRTI is smaller due to the lower numbers of patients on these regimens. A number of potentially conflicting factors have been addressed, including other factors affecting the MCV, patient weight, and dose of medication. These factors have previously not been addressed in any of the above mentioned studies [2-5].

The main weakness of the study is the retrospective nature of the data collection. This was necessary to form study groups of adequate size and ensure that data was collected at the appropriate time points. This should be counteracted by the large number of prospective patients in the study. In addition to this we do not have accurate data on alcohol consumption. However, this is often variable and not accurately reported and so it is unlikely that many studies would be able to allow for this.

Some data is lacking for haematinics, as not all patients with macrocytosis had haematinics tested within 12 months of the FBC. Of the 49 macrocytic patients taking lamivudine after exclusions, 37 had normal folate and B-12 levels demonstrated within 12 months of the abnormal MCV. 12 patients had not had haematinics within

12 months. However, of these, 6 had had normal haematinics within 3 years of the abnormal MCV and the remaining 6 had MCVs only mildly elevated with mean MCV in these 6 patients 100.9. This suggests that undiagnosed B-12 or folate deficiency is unlikely to be a significant factor.

A final note is that this study does not offer a hypothesis for the mechanism of lamivudine in causing an increase in erythrocyte MCV. One mechanism proposed in previous literature for zidovudine and stavudine is that these drugs bind non-selectively to both the HIV reverse transcriptase and the human DNA polymerase. Interference with cell DNA synthesis may lead to delayed synthesis of erythrocyte precursors and slower nuclear maturation, resulting in macrocytosis [8]. There may also be some contribution from the inhibitory effect of NRTIs on the function of erythrocyte mitochondria [9].

Conclusion

This study provides evidence to suggest that lamivudine causes an increase in the mean corpuscular volume of erythrocytes, and that this leads to macrocytosis in approximately 10% of patients. This is independent of age, sex, ethnicity, and weight and lamivudine dose. The study additionally suggests that emtricitabine can also increase the MCV, although to a smaller degree than lamivudine and with less patients reaching the threshold for macrocytosis. These findings are of clinical relevance, especially with increasing usage of lamivudine in dual regimes.

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Author Contributions

Clemency Nye: Performed literature review, collected and analysed data, and primary author of article.

Joanna Latimer: Identified concept for further research, provided critical feedback on written article.

Mark Gompels: Designed and supervised the project, oversaw analytical methods, provided critical feedback on written article.

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No funding has been received in relation to this study.

Ethics Statement

This study is original work, which has not been presented or submitted elsewhere. We have provided an accurate account of the findings and an objective discussion of its significance and are not aware of any errors or weaknesses which have not been raised in the discussion. All patient information was used in an anonymized form and therefore formal ethical approval was not required.

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