Research Article
Volume 15:05, 2024

Journal of AIDS & Clinical Research

ISSN: 2155-6113 Open Access

Increased Mean Corpuscular Volume and Macrocytosis Associated With the Use of Emtricitabine or Lamivudine in People Living With HIV Infection

Amelia Shin[1]*, Eamon Duffy[1,3], Nicola Eaddy[2] and Simon Briggs[1,4]

[1]*Department of Infectious Diseases, Auckland City Hospital, Auckland 1023, New Zealand*
[2]*Department of Haematology, Auckland City Hospital, Auckland 1023, New Zealand*
[3]*School of Pharmacy, University of Auckland, Auckland 1010, New Zealand*
[4]*Department of Molecular Medicine and Pathology, University of Auckland, Auckland 1010, New Zealand*

Abstract

Many people living with Human Immunodeficiency Virus (HIV) infection receive treatment with nucleoside reverse transcriptase inhibitors. This study's objective was to evaluate whether treatment with lamivudine and emtricitabine can result in an elevated Mean Corpuscular Volume (MCV). This was a retrospective cohort study of people who were newly diagnosed with HIV infection and received treatment with lamivudine and/or emtricitabine. MCV testing is routinely performed in the care of people living with HIV infection. This study compared each person's MCV from prior to starting anti-retroviral treatment (ART) with their MCV post-ART. Between January 2011 and June 2020, 282 people were newly diagnosed with HIV infection. 226 (80%) received emtricitabine, 45 (16%) received lamivudine and 11 (4%) received emtricitabine and lamivudine sequentially. Overall, the median MCV increased by 3.5 (IQR 2-5) fL. The median MCV increase was 3 (IQR 2 to 5) fL in the emtricitabine group, 5 (IQR 3 to 7) fL in the lamivudine group and 5.5 (IQR 4 to 6) fL in the sequential group. There was a greater MCV increase in the lamivudine group compared with the emtricitabine group ($p<0.001$). Across all groups, seven people (2.5%) developed macrocytosis (MCV ≥ 100 fL). While the increase in MCV was relatively modest and only a small percentage of people developed macrocytosis, clinicians should be aware that treatment with lamivudine and to a somewhat lesser extent emtricitabine does result in an increased MCV when compared with baseline.

Keywords: MCV change • HIV infection • Emtricitabine • Lamivudine • FTC • 3TC

Introduction

Nucleoside Reverse Transcriptase Inhibitors (NRTI) are commonly prescribed as part of combination Anti-Retroviral Treatment (ART) for People Living with HIV Infection (PLHIV). It is well described that treatment with the thymidine analogue NRTIs, particularly zidovudine and stavudine, can result in an elevated Mean Corpuscular Volume (MCV) [1]. There is however less robust evidence that suggests that treatment with lamivudine and emtricitabine (non-thymidine analogue NRTIs), can also result in an elevated MCV [2-4].

Zidovudine and stavudine are no longer recommended as first line treatment for human immunodeficiency virus (HIV) infection [5]; they have been replaced by newer NRTIs which include lamivudine and emtricitabine. With the routine use of lamivudine and emtricitabine, understanding whether their use results in an elevated MCV is important.

Aim

To assess whether treatment naïve PLHIV who started ART with a combination that included either lamivudine or emtricitabine developed an increase in their MCV and what proportion of these PLHIV developed macrocytosis (MCV ≥ 100 fL).

***Address for Correspondence:** Amelia Shin, Department of Infectious Diseases, Auckland City Hospital, Auckland 1023, New Zealand, E-mail: amelia.js.shin@gmail.com*

Received: 09 September, 2024, Manuscript No. jar-24-147608; **Editor assigned:** 11 September, 2024, PreQC No. P-147608; **Reviewed:** 23 September, 2024, QC No. Q-147608; **Revised:** 30 September, 2024, Manuscript No. R-147608; **Published:** 07 October, 2024, DOI: 10.37421/2155-6113.2024.15.1021

Methods

This study was a retrospective cohort analysis of PLHIV who were newly diagnosed with HIV infection between 1 January 2011 and 30 June 2020 and who were referred to the Infectious Disease (ID) Unit at Auckland City Hospital (ACH). The ID Unit at ACH cares for adults living with HIV infection residing in the Auckland and Northland regions of New Zealand (an adult population of approximately 1.4 million people).

Inclusion criteria

People aged 15 years and older were assessed for inclusion in this study. People were eligible if they were ART naïve, were under the care of the ID Unit at ACH, commenced an ART combination including either lamivudine or emtricitabine, and continued treatment with either medication for at least 6 months.

Exclusion criteria

The following people were excluded from the study:

1) People with insufficient medication dispensing data
2) People with insufficient laboratory data
3) People with conditions predisposing to altered MCV such as:

- Thalassaemia
- Diagnosis of lymphoma during the first 18 months of ART
- Untreated or partially treated B12 or folate deficiency
- Untreated or partially treated hypothyroidism
- Pregnancy during first 18 months of ART (as pregnancy results in an increase in MCV) [6,7]

4) People with the following abnormal laboratory parameters prior to commencing ART:

- Microcytosis (defined as a MCV of ≤ 79 fL)
- Macrocytosis (defined as MCV of ≥ 100 fL)
- anaemia (defined as haemoglobin<122 g/L for males and<108 g/L for females – these values are the lower limits of the normal range used by the Haematology Laboratory at ACH for each sex minus a 6% margin of error (3% for biological variation and 3% for analyser variation))

5) People who commenced an ART combination that included zidovudine or stavudine

6) People who stopped the lamivudine and/or emtricitabine component of their initial ART combination after less than 6 months duration

Data collection

Data were collected from clinical notes and the Auckland regional data warehouse which included laboratory and community medication dispensing records. This included; sex assigned at birth, self-reported ethnicity, date of HIV diagnosis, ART combination received, date of starting ART, haemoglobin level immediately prior to starting ART, median value of all haemoglobin results measured between 6 and 18 months after starting ART, MCV immediately prior to starting ART, median value of all MCV results measured between 6 and 18 months after starting ART (the MCV values were measured after a minimum of 6 months of ART treatment as a previous study showed that for PLHIV receiving zidovudine that the MCV rise reached steady state after 20 to 24 weeks treatment [4], B12 and folate levels taken within 2 years before starting ART to 2 years after starting ART, and thyroid function test results (thyroid-stimulating hormone and free T4) taken within 2 years before starting ART to 2 years after starting ART.

Definitions

- The lamivudine group was defined as a PLHIV who received lamivudine as a component of their initial ART regimen and did not change to an ART regimen containing emtricitabine in the first 18 months duration of ART.
- The emtricitabine group was defined as a PLHIV who received emtricitabine as a component of their initial ART regimen and did not change to an ART regimen containing lamivudine in the first 18 months duration of ART.
- The sequential group was defined as a PLHIV who received either lamivudine or emtricitabine as a component of their initial ART regimen and then changed to an ART regimen containing the alternative study anti-retroviral in the first 18 months duration of ART.

Using the above data, the change in MCV (∆MCV) for each person was calculated. PLHIV acted as their own control – the difference between the MCV value immediately prior to starting ART and the median value of all MCV results measured during the first 6 to 18 months of ART was calculated for all included people. The study duration included the first 18 months of ART however if a person stopped lamivudine or emtricitabine during the first 6 to 18 months of ART then no further data were collected from this time point. The median ∆MCV for the lamivudine group, the emtricitabine group and the sequential group was calculated.

The Mann–Whitney U test was used to assess for statistically significant differences before and after starting ART and between groups. A $P<0.05$ was deemed significant. Figures were generated with Minitab (Version 17.1.0, USA).

Ethical approval for this study was received from the Southern Health and Disability Ethics Committee (21/STH/179).

Results

In the nine-and-a-half-year period between 1 January 2011 and 30 June 2020, 453 people were diagnosed with HIV infection and subsequently referred to the ID Unit at ACH. One hundred and seventy-one people (38%) were excluded after undergoing screening (see Table, Supplemental digital content 1) leaving 282 in the study population. The most common reasons for exclusion were pre-existing anaemia (n=43), moving away from care at the ACH ID Unit clinic within six months of starting ART (n=43), insufficient laboratory test results performed during the study period (n=12) and death within six months of starting ART (n=10). Table 1 shows the characteristics of the study population.

Of the 282 people in the study population, 226 (80%) were in the emtricitabine group, 45 (16%) were in the lamivudine group and 11 (4%) were in the sequential group. In the study population, the second NRTI component of the initial ART regimen was tenofovir disoproxil fumarate (n=232) or abacavir (n=50). For the third anti-retroviral component, 147 people took an Integrase Strand Transfer Inhibitor (INSTI), 110 people took a non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) and 23 people took a Protease Inhibitor (PI). Two people took both an INSTI and a PI for their third and fourth antiretroviral component. Nineteen PLHIV changed their ART regimen during the study period as shown in Table 2.

The pre- and post-ART MCV and ∆MCV for the study population, and for the emtricitabine, the lamivudine and the sequential groups are shown

Table 1. Study population characteristics.

Demographics	
Male sex assigned at birth	93%
Median age at diagnosis (years)	39 (IQR 31-48)
Median age at initiating ART [1] (years)	40 (IQR 31-49)
Median time from diagnosis to ART initiation (days)	77 (IQR 34-241)
Ethnicity	
Māori	17 (6%)
European	174 (61.7%)
Pacific person	20 (7.1%)
Asian	48 (17%)
Middle Eastern/Latin American/African	23 (8.2%)

[1] ART: Anti-Retroviral Treatment

Table 2. People living with HIV who changed their anti-retroviral treatment regimen during the study period.

Study Antiretroviral		Second NRTI [2]	Third/Fourth Antiretroviral
Sequential group (n=11)	Emtricitabine to lamivudine (n=10)	Unchanged (n=9)	Unchanged (n=9)
		TDF [3] to ABC [4] (n=1)	NNRTI [5] changed to a PI [6] (n=1)
	Lamivudine to emtricitabine (n=1)	TDF to ABC (n=1)	INSTI [7] changed to a different INSTI (n=1)
Emtricitabine group (n=8)		Unchanged (n=8)	INSTI changed to a different INSTI (n=3)
			NNRTI changed to an INSTI (n=2)
			NNRTI changed to a different NNRTI (n=1)
			PI changed to an INSTI (n=1)
			INSTI added to a NNRTI (n=1)

[2] NRTI: Nucleoside Reverse Transcriptase Inhibitor
[3] TDF: Tenofovir Disoproxil Fumarate
[4] ABC: Abacavir
[5] NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor
[6] PI: Protease Inhibitor
[7] INSTI: Integrase Strand Transfer Inhibitor

in Figure 1. The median increase in the MCV for the study population during the study period was 3.5 (IQR 2-5) fL (P<0.00001). The median increase in the MCV during the study period was 3 (IQR 2 to 5, range -8 to 12) fL in the emtricitabine group (P<0.00001), 5 (IQR 3 to 7, range -0.5 to 10) fL in the lamivudine group (P<0.00001) and 5.5 (IQR 4 to 6, range 1 to 7) fL in the sequential group (P=0.006). Comparing the emtricitabine group with the lamivudine group, there was a larger increase in the MCV in the lamivudine group (P<0.001).

Of the 226 people in the emtricitabine group, 192 (85%) had an increase in their MCV over the duration of the study, and five (2.2%) developed macrocytosis (MCV ≥ 100 fL). Of these 226 people, 90 had a B12 level, 87 had a folate level and 132 had a thyroid function test performed between two years before and two years after their HIV diagnosis, all of which were normal. Of the five people who developed macrocytosis, three people had a B12 level, a folate level and a thyroid function test performed within a year of developing the macrocytosis; all these tests were normal. The remaining two did not have these tests performed. Of the 45 people in the lamivudine group, 43 (96%) had a rise in their MCV over the duration of the study, and two (4.7%) developed a macrocytosis (MCV ≥ 100 fL). Of these 45 people, 13 had a B12 level, 13 had a folate level and 24 had a thyroid function test performed between two years before and two years after their HIV diagnosis all of which were normal. Of the two people who developed a macrocytosis, one person had a B12 level, a folate level and a thyroid function test performed within a year of developing the macrocytosis; all these tests were normal. The other person did not have these tests performed.

Of the 11 people in the sequential group, all 11 (100%) had a rise in their MCV over the duration of the study but no one developed macrocytosis (MCV ≥ 100 fL). Of this group, four had a B12 level, four had a folate level and seven had a thyroid function test performed between two years before and two years after their HIV diagnosis, all of which were normal.

To examine the possibility that differences in sex or age may have resulted in more or less of an increase in the MCV, sex and age differences for the study population and the emtricitabine group were assessed in a posthoc analysis. There was no difference in the median change in the study population MCV comparing males (n=261) with females (n=21), with median MCV increases of 3 and 4fL respectively (P=0.72). There was no difference in the median change in the emtricitabine group' MCV comparing males (n=206) with females (n=20), with median MCV increases of 3 and 3.75fL respectively (P=0.38). The median increases in MCV by age for the study population and for the emtricitabine group are shown in Table 3. There was a difference in the change in MCV in the study population when comparing those aged 15 to 59 years with those aged ≥ 60 years, with a greater MCV increase in those aged ≥ 60 years (*P*=0.03). There was a difference in the change in MCV in the emtricitabine group when comparing those aged 15 to 59 years with those aged ≥ 60 years, with a greater MCV increase in those aged ≥ 60 years (*P*=0.02). No analysis of possible differences in sex or age was undertaken for the lamivudine group as there was only one person aged ≥ 60 years and no females in this group.

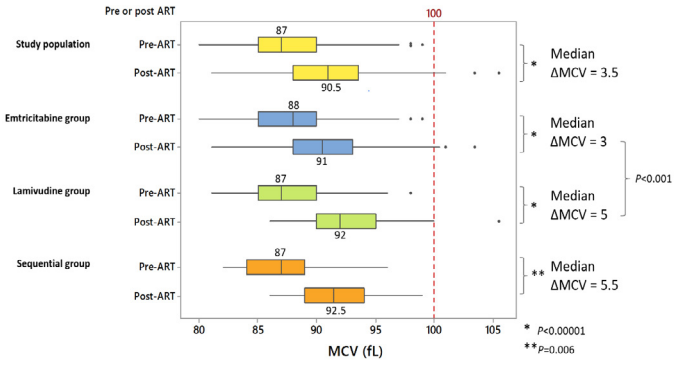

Figure 1. Pre- and Post-ART MCV and ΔMCV for the study population, and the emtricitabine, lamivudine and sequential groups.

ART: anti-retroviral treatment, MCV: mean corpuscular volume, ΔMCV: change in mean corpuscular volume.

Table 3. Median increase in mean corpuscular volume by age (at the time of starting anti-retroviral treatment) for the study population and emtricitabine groups.

Group	Age (years)								Total number
	15 to 29		30 to 44		45 to 59		≥ 60		
	N	Median MCV increase	N	Median MCV increase	N	Median MCV increase	N	Median MCV increase	
Total population	52	3.5	129	3	78	4	23	5*[8]	282
Emtricitabine group	41	3	105	3	60	3.25	20	4.5**[9]	226

[8] *P=0.03 when comparing those aged ≥ 60 years with those aged 15 to 59 years
[9] **P=0.02 when comparing those aged ≥ 60 years with those aged 15 to 59 years

The median pre-ART haemoglobin level was 144 g/L. This did not differ significantly across the three groups. During the study period the median haemoglobin level of the study population increased, with a median increase of 5 g/L (P<0.00001). The median increase in the haemoglobin level was 5 (IQR -1 to 13) g/L in emtricitabine group (P<0.00001), 7.5 (IQR 1-11) g/L in lamivudine group (*P*=0.0001) and 8 (IQR 2-18) g/L in the sequential group (P=0.06). Using the study definition, three people developed anaemia during the post-ART study period. These three were male and were all in the emtricitabine group. Their haemoglobin levels and MCV pre- and post-ART were; haemoglobin 138 to 98, 139 to 93, 137 to 110 g/L and MCV 89 to 92, 96 to 100, and 93 to 98 fL respectively. The first person underwent coronary artery bypass grafting surgery with large volume blood loss in the first 12 months of ART at the time of developing anaemia. The anaemia resolved within 6 months of this surgery (he had normal B12 and folate levels in the post-ART study period, but no other investigations performed to investigate the anaemia). The second person was diagnosed with infective endocarditis in the first 12 months of ART, with heart valve surgery five months later. This person had a normal haemoglobin level at the time of diagnosis of endocarditis however developed anaemia at the time of the heart valve surgery. The anaemia resolved within three months of this surgery (he did not have any investigations performed to investigate the anaemia). The third person remained anaemic for the entire duration that they took emtricitabine, no additional medical issues were noted during the post-ART study period and their anaemia was not investigated during this time.

Discussion

This study showed that ART-naïve PLHIV who started treatment with either an emtricitabine or lamivudine containing ART regimen developed an increase in their MCV 6 to 18 months after starting this treatment. Treatment with lamivudine resulted in a larger increase in MCV when compared with emtricitabine (the median increase was 5 fL in the lamivudine group and 3 fL in the emtricitabine group). 85%of the emtricitabine group and 96% of the lamivudine group developed and increased MCV, 2.2% and 4.7% respectively developed macrocytosis.

These findings are similar to the available data on macrocytosis associated with the use of lamivudine or emtricitabine. A retrospective study assessing change in MCV in PLHIV taking NRTIs, showed that eight people who received lamivudine for at least 24 weeks, without zidovudine or stavudine, developed a mean MCV rise of 9.5% (P=0.0007 when compared with those not receiving ART) [4]. A retrospective study of 60 PLHIV, none of whom was taking zidovudine or stavudine, showed that macrocytosis was associated with lamivudine use (P=0.001) [3]. A retrospective study from the UK comparing 456 PLHIV receiving lamivudine with 420 receiving emtricitabine and 63 not receiving a NRTI known to affect the MCV, showed mean MCVs of 94.1, 91.8 and 89.8 fL respectively (P<0.0001 when comparing the lamivudine group with either of the other two groups) [2]. The higher

mean MCVs of 4.3 and 2 fL seen in the lamivudine and emtricitabine groups respectively when compared with the group not receiving a NRTI known to affect the MCV were similar to our findings of a median increase of 5 and 3 fL in the lamivudine and emtricitabine groups respectively.

Mitochondrial toxicity has been proposed as a mechanism by which NRTIs produce a number of adverse effects such as skeletal myopathy, cardiomyopathy, neuropathy, lactic acidosis, and lipodystrophy. This mechanism also potentially explains why some NRTIs result in an increase in MCV [8]. NRTI related mitochondrial toxicity is thought to result from one or more of the following; the direct inhibition of DNA polymerase-γ (pol- γ), the net effect of mitochondrial DNA chain termination that occurs after NRTI incorporation and then to a lesser extent NRTI removal by the exonucleolytic function of DNA pol- γ, and the subsequent reduced fidelity of DNA synthesis [9]. This reduction in DNA synthesis is felt to result in the slower maturation of erythrocytes [10,11]. Less mature erythrocytes, which have an increased MCV when compared with more mature erythrocytes, may then be released into the peripheral blood resulting in a rise in overall MCV. The efficiency with which DNA pol- γ is able to incorporate or remove particular NRTIs into or from mitochondrial DNA differs depending on the NRTI [12]. Stavudine has been found to be most efficiently incorporated followed by abacavir, lamivudine and zidovudine. Lamivudine has been found to be most efficiently removed (with 60 to 70% of the incorporated nucleoside removed) followed by stavudine, zidovudine and abacavir (with less than 20% of these three incorporated nucleosides removed). The overall differing net effects of incorporation and removal of particular NRTIs may explain, at least to some degree, the differing extent of MCV rise observed with the use of particular NRTIs. This however does not appear to be the sole explanation of the MCV rise given that although abacavir is the nucleoside with the second most efficient incorporation and a low level of removal, its use has not been associated with the development of macrocytosis [1]. Lamivudine is more efficiently incorportated into mitochondrial DNA by DNA pol-γ than emtricitabine [13] resulting in lamivudine's higher mitochondrial toxicity. This may provide some explanation as to why treatment with lamivudine in this study resulted in a larger increase in MCV when compared with emtricitabine.

We observed that the MCV increase in the study population and in the emtricitabine group was greater in those aged ≥ 60 years. Emtricitabine and lamivudine are both predominantly renally excreted. Age-related reduction in renal excretion results in an increased exposure to both of these NRTIs [14] and therefore the possibility of increased toxicity. Also with age, bone marrow cellularity decreases and there is a variable decline in bone marrow activity [15]. The combined effect of possible increased toxicity related to reduced renal excretion and the decline in bone marrow activity may explain the greater MCV increase we observed in those aged ≥ 60 years. The effect of lamivudine on MCV was found to be independent of age in the only other study [2] that has assessed this potential association previously, so this finding needs to be assessed further in future studies.

During the study period, we found that the haemoglobin level of the study population increased, with a median increase of 5 g/L. An increase in haemoglobin levels during first year of ART has been previously reported [16]. Reasons for the increase in the haemoglobin level in the study are likely multifactorial and probably included HIV viral suppression and the general health gains that result from this; there is evidence that the HIV virus can have a direct role in causing anaemia [17]. Unlike zidovudine,lamivudine and emtricitabine have not been described as causing anaemia [1]. Three people receiving emtricitabine developed anaemia in the post- ART study period. Two of these people had an identifiable cause for their anaemia and the anaemia resolved while they continued to receive emtricitabine. The third person did not have their anaemia investigated so it is not possible to exclude emtricitabine as a possible contributing cause.

Given that a relatively modest increase in MCV was observed and only a small proportion of people developed macrocytosis in the study, people who are receiving emtricitabine or lamivudine who develop macrocytosis should be investigated for other potential causes. These investigations should include B12 and folate levels, thyroid function testing, consideration of haemolysis, myelodysplasia or liver disease, as well as the assessment of alcohol consumption. If standard testing does not demonstrate an alternate cause, then the macrocytosis could be presumed to be secondary to the emtricitabine or lamivudine.

This study has several strengths. We used each individual person as their own control; this enabled us to measure the ΔMCV for each person after they commenced emtricitabine or lamivudine rather than comparing the MCV of groups of people receiving different NRTIs, as previous studies assessing the impact of lamivudine or emtricitabine have done. The study design is relatively straightforward and so could be replicated in other settings if clinicians required confirmation of our findings in their setting. We attempted to exclude people who had a condition that could have impacted on their MCV. This study included a moderate number of PLHIV who were treated at the same clinic in relatively uniform ways.

There are several limitations of this study. Given its retrospective design, we were not able to access some data. This study assumed full adherence with the prescribed ART (except when there was clear documentation of non-adherence in five PLHIV who were excluded), however a degree of non-adherence would only have lessened the degree of MCV increase. We were not able to collect data on alcohol consumption, therefore we cannot exclude the possibility that a significant alteration in a particular person's alcohol consumption may have resulted in a change in their MCV thereby confounding their individual result. We did not collect data on the concurrent use of non-ART medication known to cause macrocytosis. The study population consisted predominantly of European males (reflecting the population of newly diagnosed PLHIV who were receiving care at our clinic during the study period) therefore there may need to be some caution applying the findings of this study to PLHIV of other ethnicities and females although a previous study did not find an association between the effect of lamivudine on MCV and either ethnicity or sex [2].

Conclusion

The majority of PLHIV receiving treatment with emtricitabine or lamivudine would be expected to develop a relatively modest increase in their MCV and a small proportion (less than 5%) would be expected to develop macrocytosis within 6 to 18 months of starting either of these NRTI. While the increase in MCV in this study was relatively modest, clinicians should be aware that treatment with lamivudine and to a somewhat lesser extent emtricitabine does result in an increased MCV.

Authorship Contribution Statement

Amelia Shin: Formal Analysis, Investigation, Methodology, Data Curation, Writing – Original Draft, Visualisation

Eamon Duffy: Conceptualisation, Methodology, Data Curation, Writing – Review & Editing

Nicola Eaddy: Methodology, Writing – Review & Editing

Simon Briggs: Conceptualisation, Investigation, Methodology, Writing – Review & Editing'

All authors have read and approved the text as submitted to AIDS Clin Res.

Author Disclosure

None declared.

Funding Statement

None declared.

Conflict of Interest

None.

References

1. Kufel, W. D., C. M. Hale, E. F. Sidman and C. E. Orellana, et al. "Nucleoside Reverse Transcriptase Inhibitor (NRTI) associated macrocytosis." *Int J Virol AIDS* 3 (2016): 18.
2. Nye, C. and J. Latimer. "Gompels M. Macrocytosis associated with lamivudine and emtricitabine use in patients with HIV." *J AIDS Clin Res* 12 (2020).
3. Khawcharoenporn, Thana, Cecilia M. Shikuma, Andrew E. Williams and Dominic C. Chow. "Lamivudine-associated macrocytosis in HIV-infected patients." *IJStdAids* 18 (2007): 39-40.
4. Steele, Richard H., Gary L. Keogh, John Quin and Suran L. Fernando, et al. "Mean Cell Volume (MCV) changes in HIV-positive patients taking Nucleoside Reverse Transcriptase Inhibitors (NRTIs): A surrogate marker for adherence." *IJStdAids* 13 (2002): 748-754.
5. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv
6. Chanarin, I., I. R. McFadyen and R. Kyle. "The physiological macrocytosis of pregnancy." BJOG: An International Journal of Obstetrics & Gynaecology 84 (1977): 504-508.
7. Rayis, Duria A., Mohamed A. Ahmed, Hafez Abdel-Moneim and Ishag Adam, et al. "Trimester pattern of change and reference ranges of hematological profile among Sudanese women with normal pregnancy." *Clin Pract* 7 (2017).
8. Gerschenson, Mariana and Kees Brinkman. "Mitochondrial dysfunction in AIDS and its treatment." *Mitochondrion* 4 (2004): 763-777.
9. Lewis, William, Brian J. Day and William C. Copeland. "Mitochondrial toxicity of NRTI antiviral drugs: An integrated cellular perspective." *Nat Rev Drug Discov* 2 (2003): 812-822.
10. Romanelli, Frank, Kerry Empey and Claire Pomeroy. "Macrocytosis as an indicator of medication (zidovudine) adherence in patients with HIV infection." *AIDS Patient Care STDS* 16 (2002): 405-411.
11. Sternfeld, Thomas, Antje Lorenz, Mathias Schmid and Angelika Schlamp, et al. "Increased red cell corpuscular volume and hepatic mitochondrial function in NRTI-treated HIV infected patients." *Curr HIV Res* 7 (2009): 336-339.
12. Lim, Susan E. and William C. Copeland. "Differential incorporation and removal of antiviral deoxynucleotides by human DNA polymerase γ." *J Biol Chem* 276 (2001): 23616-23623.
13. Sohl, Christal D., Michal R. Szymanski, Andrea C. Mislak and Christie K. Shumate, et al. "Probing the structural and molecular basis of nucleotide selectivity by human mitochondrial DNA polymerase γ." Proc Natl Acad Sci 112 (2015): 8596-8601.
14. De Sousa Mendes, M. and Manoranjenni Chetty. "Are standard doses of renally-excreted antiretrovirals in older patients appropriate: A PBPK study comparing exposures in the elderly population with those in renal impairment." *Drugs in R&D* 19 (2019): 339-350.
15. Lipschitz, D. A., K. B. Udupa, K. Y. Milton and C. O. Thompson. "Effect of age on hematopoiesis in man." (1984): 502-509.
16. Kowalska, Justyna D., Amanda Mocroft, Anders Blaxhult and Robert Colebunders, et al. "Current hemoglobin levels are more predictive of disease progression than hemoglobin measured at baseline in patients receiving antiretroviral treatment for HIV type 1 infection." *AIDS Res Hum Retroviruses* 23 (2007): 1183-1188.
17. Redig, Amanda J. and Nancy Berliner. "Pathogenesis and clinical implications of HIV-related anemia in 2013." Hematology 2013, the American Society of Hematology Education Program Book 2013 (2013): 377-381.

How to cite this article: Shin, Amelia, Eamon Duffy, Nicola Eaddy and Simon Briggs. "Increased Mean Corpuscular Volume and Macrocytosis Associated With the Use of Emtricitabine or Lamivudine in People Living With HIV Infection." *AIDS Clin Res* 15 (2024): 1021.