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Nucleoside Reverse Transcriptase Inhibitor (NRTI) Associated Macrocytosis

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Abstract

Macrocytosis has been associated with several disease states, vitamin deficiencies, and medications, with nucleoside reverse transcriptase inhibitors (NRTIs) being a less commonly identified cause. NRTIs are frequently utilized as the two-drug backbone for the treatment of Human Immunodeficiency Virus (HIV). Amongst the NRTI drug class, zidovudine (AZT) and stavudine (d4T) are the most widely reported cause of macrocytosis. Fortunately, AZT and d4T have become less commonly used therapies, as newer NRTIs with improved toxicity profiles have emerged. Fewer data exist to describe the association between macrocytosis and other NRTI agents. The primary objective of this article is to review NRTI-associated macrocytosis, including incidence, timing of onset, degree of rise in mean corpuscular volume, and association with concomitant anemia.

Keywords

Nucleoside Reverse Transcriptase Inhibitor (NRTI), Macrocytosis, Mean Corpuscular Volume (MCV), Human immunodeficiency virus (HIV), Antiretroviral therapy

Introduction

The availability of potent combination antiretroviral therapy (ART) has significantly increased the lifespan of individuals infected with human immunodeficiency virus (HIV) [1]. Current treatment guidelines recommend a combination of at least three antiretroviral drugs for optimal suppression of viral load and restoration of immune function [2]. The nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) remain a common component of these treatment regimens. NRTIs are analogues of native nucleosides which were the first antiretrovirals to see widespread clinical use. NRTIs function as chain terminators, blocking the viral RNA-dependent DNA polymerase, reverse transcriptase (RT), from synthesizing complementary DNA from HIV RNA [3,4]. After intracellular phosphorylation steps, NRTIs can also inhibit the activity of normal cellular DNA polymerases, such as the mitochondrial DNA

polymerase-γ (pol-γ) [3,4]. It is this NRTI-associated inhibition of mitochondrial function that is responsible for many of the drug-specific adverse effects [5]. NRTIs are among the most commonly utilized drug classes in Highly Active Antiretroviral Therapy (HAART) [2]. Currently recommended first-line treatment options include two NRTI agents, also known as the backbone of the regimen, combined with a protease inhibitor (PI) or an integrase strand transfer inhibitor (INSTI) [2].

Erythrocyte volume is automatically measured in most laboratories as part of the complete blood count (CBC) lab test. Macrocytosis is a term commonly used to describe the increase in the average size of red blood cells or mean corpuscular volume (MCV) above 100fl [6]. In the general population, the prevalence of this red blood cell abnormality is estimated to be about 2% [7]. It is typically a benign process that can be problematic if also associated with anemia (hemoglobin < 12 g/dL in women and < 13 g/dL in men) [8]. However, approximately 40% of macrocytosis cases present with co-morbid anemia [7]. Common causes of macrocytosis include nutritional deficiencies (i.e. vitamin B12 or folate), cirrhosis of the liver, alcohol abuse, hypothyroidism, and drugs [9,10]. Some drugs commonly associated with the development of macrocytosis include certain chemotherapeutic agents (i.e. hydroxyurea), antimicrobials (i.e. pyrimethamine, sulfamethoxazole, trimethoprim, and valacyclovir), triamterene, phenytoin, and the NRTIs [9]. Providers who are not specialists in the care of HIV patients may be unaware of the potential for NRTI-related macrocytosis and perform further diagnostic workup when it is generally not necessary [11].

The prevalence of macrocytosis has not been established in the HIV-positive population, yet the virus itself is known to cause a number of hematologic disturbances including anemia, neutropenia, thrombocytopenia, and altered coagulation parameters [12]. These disturbances are due to a suppressive effect of the virus on hematopoiesis through an altered expression and production of erythropoietin and granulocyte-colony stimulating factor [13]. Mechanistically, then, HIV is more likely to be associated with

Table 1: Key Studies that Investigated NRTI-Associated Macrocytosis

Authors	Study design	Population (n)	NRTI(s) assessed (n)	NRTI(s) Associated with Macrocytosis
Romanelli et al. [4]	Retrospective, single-center chart review	HIV-infected patients (164)	AZT (71)	AZT
Genné et al. [6]	Retrospective, single-center cohort study	Cases with macrocytosis (30)	ddI (4/30)	d4T
		Controls without macrocytosis (60)	d4T (28/30)	
Eyer-Silva et al. [11]	Retrospective, single-center study	A: AZT- naïve (81)	d4T (115)	d4T
		B: AZT-experienced (34)		
		All Patients on d4T		
Khawcharoenporn et al. [12]	Retrospective, single-center study	60 HIV-infected patients not on AZT or d4T	3TC (n/r)	3TC
			ABC (n/r)	
			TDF (n/r)	
Petersen et al. [14]	Retrospective, multicenter chart review	590 HIV-infected patients	All AZT (527)	AZT
			AZT monotherapy (412)	d4T
			All d4T (40)	3TC
			All 3TC (139)	
			All ddI (28)	
			ddI monotherapy (11)	
Diop et al. [15]	Retrospective, transversal study	112 HIV-infected patients	3TC (150)	AZT
			d4T (21)	d4T
			AZT (83)	3TC
			ABC (84)	
			TDF (60)	
			ddI (33)	
Steele et al. [17]	Retrospective, single-center chart review	61 HIV-infected patients	3TC (8)	AZT
			AZT (30)	d4T
			d4T (41)	3TC
Volberding et al. [22]	Double-blind, multicenter, placebo controlled trial	1637 HIV-infected patients	AZT (1090)	AZT
			Placebo (547)	
Richman et al. [27]	Double-blinded, placebo controlled trial	278 HIV-infected patients	AZT (143)	AZT
			Placebo (135)	
Ahmad et al. [33]	Retrospective, single-center case series	17 HIV-infected patients	d4T	d4T
Martin et al. [31]	Retrospective, single-center chart review	91 HIV-infected patients	d4T	d4T

a normocytic or microcytic anemia of chronic disease than with macrocytosis. One study in particular demonstrated an inverse association between HIV viral load and elevated MCV in HIV-infected patients, with all cases of macrocytosis occurring in patients receiving HAART [6]. Thus, the available data suggest that macrocytosis in HIV-infected patients is more likely to be caused by ART than the infection itself. There does not appear to be an association between PIs or Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and macrocytosis [12,14]. It is important to note, however, many HIV-infected patients have a number of the aforementioned risk factors, and thus have an increased likelihood of presenting with a macrocytosis with or without anemia, especially if on treatment with NRTIs.

A majority of the literature on NRTI-associated macrocytosis pertains to the thymidine analogs (stavudine and zidovudine), yet it is less clear if non-thymidine NRTIs (abacavir, emtricitabine, lamivudine, tenofovir, and didanosine) may induce macrocytosis as well. It has been proposed that treatment with any NRTI may induce a macrocytosis ($p < 0.001$) [15]. We performed a MEDLINE search to investigate the relative potential for macrocytosis amongst the NRTI drug class. Herein, we report the results of the literature search, with our findings summarized in Table 1.

Thymidine Analogs

Zidovudine (AZT) and stavudine (d4T) are members of the sub-class of NRTIs referred to as the thymidine analogs [16]. Steele and colleagues noted a linear rise in MCV during treatment with these two agents, plateauing at 20-24 weeks [17]. The mechanism by which this occurs is still unclear. However, both drugs compete with natural deoxynucleoside triphosphates for binding to both HIV RT and, to a lesser extent, human DNA polymerase and mitochondrial pol-γ. Inhibition of cellular DNA synthesis can result in impaired synthesis of erythrocyte precursor cells and delayed nuclear maturation in bone marrow, subsequently leading to macrocytosis [4,18]. Notably, AZT

and d4T are amongst those NRTIs with the highest incorporation rates by pol-γ relative to other NRTIs, indicating an increased risk of mitochondrial toxicity with these agents [19,20].

Zidovudine (AZT)

AZT-associated macrocytosis is well-documented and comprises the earliest reports of this hematologic abnormality secondary to NRTI utilization. Macrocytosis occurs in essentially all patients treated with AZT and has even been used as a marker of adherence to ART [4,21-23]. Collectively, these studies have documented a predictable and reliable increase in MCV secondary to adherence to regimens containing AZT. Because strict adherence to ART is instrumental in achieving the goals of virologic suppression and good outcomes, a reliable laboratory marker of adherence such as MCV has utility in predicting therapeutic success. MCV can be used to specifically monitor for adherence to AZT and can complement viral load monitoring which is considered a standard monitoring tool to ensure adherence with the entire ART regimen. Macrocytosis usually develops greater than 6 weeks after AZT initiation [11,23,24], but can occur as early as 2-4 weeks [25-27].

Richman et al. conducted a double-blinded, placebo-controlled trial of 282 HIV-infected patients, comparing AZT toxicities with placebo [27]. The authors found that 100 of 145 (69%) subjects that received AZT developed macrocytosis compared to none of the 137 subjects who received placebo. The overall mean change in MCV by week 22 was + 17.62 fl. Additionally, a reduction in hemoglobin was first appreciable as early as two weeks in 5% of AZT recipients, affecting 34% by six weeks. This was further complicated by the development of anemia requiring blood transfusions in 31% of AZT recipients compared to 11% in the placebo group ($p < 0.05$). Drastically low hemoglobin levels below 7.5 g/dL were observed in 24% of AZT recipients compared to 4% of placebo ($p < 0.001$). Hematologic toxicity due to AZT was prevalent for not only red blood cells, but all cell lines in this trial. This was the first of many

studies identifying a relationship between AZT and macrocytosis, and highlighted an association with anemia as well.

In a retrospective review of 100 inpatients with macrocytosis, Snower et al. found an association between AZT use and macrocytosis, noting that 44 of the 47 patients with both AIDS and macrocytosis were being treated with AZT [28]. Only three of these 44 patients had a concomitant vitamin B12 deficiency. They concluded that AZT use was a prominent cause of macrocytosis in an inpatient population during a time when AZT was a cornerstone of HIV therapy. Several other studies confirm a significant association between AZT use and macrocytosis [4,17,22-26,29,30].

Another retrospective review of 164 HIV-infected patients compared patients prescribed AZT for 8 weeks to controls, who were AZT-free for 8 weeks or more in order to determine if macrocytosis could be used as a marker of treatment adherence [4]. The incidence of macrocytosis was significantly greater in the subjects versus controls group (78% vs. 32.6%, p < 0.001). Seventy-seven percent of the subjects with macrocytosis were determined to be adherent by physician or pharmacist documentation in the medical record. Macrocytosis as a marker of AZT adherence was also assessed by Mugisha et al. in an observational study within a randomized controlled trial [23]. The authors noted a mean overall increase of 2.5% (95% CI: 2.0-3.0) and 12.6% (95% CI: 11.2-13.9) at 4 and 12 weeks, respectively. Interestingly, a rise in MCV of 8% by week 12 correctly identified virologic responders 90% of the time, illustrating the prevalence of macrocytosis in AZT-adherent patients. Supplemental to these findings, Rivas and colleagues found that MCV remained relatively unchanged during the first 8 weeks of AZT treatment in 47 adherent patients receiving AZT, lamivudine, and lopinavir-ritonavir, and was therefore unusable for measuring adherence during that time period [24]. However, red cell distribution width (normal 13.1 to 15.2%) significantly increased over the first two months (17.7% at one month and 19.8% at two months; P<0.001 compared to baseline) of treatment before declining back to normal levels at four months. This in combination with a gradual rise in mean MCV from baseline of 87 fl to 110 fl over 4 months of treatment indicates a shift in red cell population towards a macrocytic predominance. Given that the average lifespan of an erythrocyte is approximately 120 days, these findings indicating a later onset of significant AZT-associated macrocytosis are not surprising [23]. More recently, Kim and colleagues retrospectively characterized the association between MCV and laboratory markers of response to ART, including CD4 count and HIV-RNA [29]. Patients receiving AZT-based ART had higher MCV levels (111.6 ± 7.0 vs. 97.8 ± 7.0, p < 0.001) and a higher incidence of macrocytosis (95.3% vs. 38.2%, p < 0.001). They also identified a weak to moderate association between CD4% and MCV levels in patients receiving AZT (r = 0.338, p < 0.001), indicating that MCV levels may be used as a surrogate marker to evaluate adherence to AZT-based regimens.

Petersen et al. conducted a retrospective chart review of 590 patients to investigate macrocytosis after various NRTI regimens at 90 days of ART [14]. AZT monotherapy significantly increased the MCV by an average of 10.52 fl, and all patients treated with AZT had a significant rise in MCV of 10.83 fl. Similarly, Steele et al. found an average MCV increase of 26.1% from baseline in the 18 subjects adherent to AZT over a 24-week period [17]. A rise in %MCV was strongly correlated with adherence to AZT (Spearman R = 0.82, p < 0.05). Volberding et al. conducted a double-blind, multicenter, placebo-controlled trial of 1,637 subjects randomized to receive AZT (500mg or 1500mg) or placebo [22]. The primary outcome was to assess efficacy of AZT, while secondary outcomes included toxicity endpoints. MCV was monitored regularly throughout the study and was elevated in less than 10% of the subjects receiving placebo (n = 547), whereas it was consistently elevated regardless of dose in subjects receiving AZT (n = 1090). Median MCV was 89 fl in the placebo group compared to 110 fl at 20 weeks in those receiving AZT. The authors did not comment on the statistical significance of mean elevation in MCV, nor did they characterize an association between dose and degree of macrocytosis.

The evidence provided by these studies is strongly suggestive of a relationship between AZT use and development of macrocytosis, both with and without anemia. This effect does not appear to be dose-related. Based on currently available data, elevated MCV could be utilized by clinicians as a marker of adherence and response to AZT rather than perhaps potentially unpractical therapeutic drug monitoring (TDM) or reliance on patient-reported adherence.

Stavudine (d4T)

Macrocytosis associated with d4T is also well-acknowledged in the literature, but raises the MCV to a lesser extent than AZT [4,11,14,17,31]. The first recognized association between d4T and macrocytosis was in a phase I trial of d4T monotherapy, which observed a dose-related increase in MCV without anemia in 41 enrolled patients after 18 weeks of treatment [32]. The following studies confirm d4T-associated macrocytosis in the absence of anemia.

A small retrospective study by Ahmad et al. reported a gradual increase in MCV with duration of treatment in 16 patients on d4T with no other predisposing factors for macrocytosis [33]. The mean increase in MCV was as follows: 3.95 fl at 0-4 weeks (95% CI 1.15-6.76), 4.71 fl 4-8 weeks (95% CI 0.37-9.04), 8.41 fl at 8-12 weeks (95% CI 0.89-15.99), 10.47 fl at 12-20 weeks (95% CI 4.10-16.84), and 12.44 fl at greater than 20 weeks (95% CI 6.47-18.42). Furthermore, Steele and colleagues compared AZT, d4T, and 3TC to no drugs in terms of %MCV change [17]. MCV levels rose 20.5% for the 35 adherent patients on d4T-containing regimens, which was significantly smaller compared to AZT (26.1%, p = 0.003). Consistent with these findings, Petersen et al. determined d4T raised the MCV by an average of 11.07 fl after 3 months of therapy [14].

Martin and colleagues retrospectively reviewed charts of 91 patients whose treatment regimen included d4T [31]. Macrocytosis was observed in 73% of patients on d4T-based regimens over the course of at least 3 months of treatment duration. The mean MCV at initiation of d4T treatment was 96.3 fl (range: 78.9-118.8 fl) and increased to 104.6 fl after 3 months of treatment (range: 79.0-122.1 fl). The mean increase in MCV was 9.3 fl (range: -10.3 to 29.3 fl; p < 0.05). The authors further assessed the effect of previous exposure to AZT. Fifty-three percent of patients were AZT-naive before d4T initiation. This group had a mean MCV of 89.5 fl (range: 78.9-99.5 fl) at initiation of therapy and a mean increase in MCV of 13.9 fl (range: 0.1-29.4 fl; p < 0.05). In comparison, patients previously receiving AZT had a mean baseline MCV of 103.9 (range: 81.3-118.8 fl), and only saw a mean increase in MCV of 2.2 fl (range, 10.3-20.2 fl; p = 0.11). None of the patients in this study developed anemia secondary to treatment with d4T. In fact, these authors found a small, but statistically significant, increase in hemoglobin levels. The mean baseline hemoglobin level was 13.4 g/dL (range: 8.4-17.2 g/dL), which rose to 14.2 g/dL after 3 months of treatment (range: 10.1-17.1 g/dL; p < 0.05). While d4T treatment is associated with macrocytosis, this hematologic irregularity does not appear to cause macrocytic anemia as has been reported with AZT [27].

Eyer-Silva et al. similarly performed a retrospective analysis in which 81 AZT-experienced patients (Group A) and 34 AZT-naïve patients (Group B) were initiated on d4T for 24 weeks [11]. In group A, the mean MCV after 24 weeks was 109.18 ± 8.31 fl and the mean change from baseline was -4.5 ± 7.7 fl (p < 0.001; 95% CI: -6.21 to -2.29). In group B, the mean MCV after 24 weeks of treatment was 105.31 ± 7.87 fl and the mean change from baseline was $+16.71 \pm 8.04$ fl (p < 0.001; 95% CI: 13.76-19.66). This study further supports d4T-associated macrocytosis, but not to the degree that AZT can inflict.

Genné and colleagues retrospectively investigated AZT-naïve, HIV-infected patients [6]. Thirty subjects with MCV > 100 fl were compared to 60 randomly selected subjects with MCV < 99 fl. There was an association between macrocytosis and d4T use alone or in combination with other ART (28/30 cases vs 15/60 controls; OR 40.6, 95% CI: 5.1-325.2, p < 0.001). Also, the hemoglobin levels among cases (mean: 13.5 g/dL) were similar to that of controls (13.0 g/dL),

supporting the findings by Martin et al. that d4T is not associated with a macrocytic anemia.

Overall, d4T treatment is clearly associated with macrocytosis, yet differs in severity from AZT even though both drugs are classified as NRTI thymidine analogs. Stavudine (d4T) does not produce macrocytosis to the degree that AZT does, nor does d4T appear to be associated with anemia or reduction in hemoglobin levels as is seen with AZT-treatment.

Non-thymidine Analogs

While the association between thymidine analogs and macrocytosis is well-referenced, there are fewer published reports documenting an association, or lack thereof, with non-thymidine analogs.

Lamivudine (3TC)

After careful review of available literature, there have been limited studies confirming 3TC-associated macrocytosis. In phase II and III clinical trials, 3TC monotherapy was uncommonly associated with macrocytosis and was only seen at doses at least twice as high as those currently used in clinical practice [31]. In a retrospective analysis by Steele et al., 8 patients received 3TC without d4T or AZT [17]. Patients on 3TC alone showed a small %MCV rise above baseline (9.5%), which was significant compared to patients on no therapy (p = 0.0007). Furthermore, if individual patients changed from an AZT/3TC combination to an AZT/ddI combination, a fall in the %MCV rise was appreciated.

In a retrospective, single-center study by Khawcharoenporn et al., macrocytosis was found to be associated with ART, and specifically with 3TC use [12]. The authors reviewed 60 HIV-infected patients not being treated with AZT or D4T. Lamivudine was found to be strongly associated with macrocytosis (OR = 24.6, 95% CI: 2.9-3223.0, p = 0.001). A logistic regression analysis revealed that lamivudine use was also an independent factor associated with macrocytosis (p = 0.004). The degree of change in baseline MCV was not reported. The authors concluded that 3TC was strongly associated with macrocytosis despite the small sample size, and that this association may be related to 3TC's effect on erythrocyte synthesis that is similarly observed with AZT or d4T treatment.

In 2006, Diop et al. conducted a retrospective, transversal study in order to test the accuracy of glycated hemoglobin in predicting mean glycemia in 112 HIV-infected patients [15]. As a secondary finding, the authors stated that treatment with any NRTI was significantly associated with macrocytosis. A logistic regression analysis including all NRTIs used by more than 10 patients revealed that only 3TC (OR 2.5, 95% CI: 1.1-5.6, p = 0.03), AZT (OR 16.3, 95% CI: 6.9-38.6, p < 0.0001), and d4T (OR 8.7, 95% CI: 2.9-26.0, p = 0.0001) remained significantly associated with macrocytosis. Although a majority of patients were on 3TC (150/197), the authors did not elaborate on the percentage of patients taking 3TC that were also taking AZT or d4T. As such, their findings do not demonstrate a clear association between 3TC and macrocytosis given that 3TC and AZT are co-formulated and often used concomitantly as a backbone of HAART. In contrast, Petersen et al. found a non-significant increase in MCV by an average of 12.5 fl in the 139 patients receiving 3TC in a retrospective study of 590 patients adherent to ART for 90 days (95% CI: 1.323284) [14]. Again, nearly all patients on 3TC were also taking AZT or d4T. Genné et al. shared a similar observation [6].

Overall, there are limited data that associate 3TC use with macrocytosis. Many of the studies included patients that may have also been taking AZT or d4T, and thus a clear association cannot be concluded. More studies are needed to clarify the presence and degree of this relationship.

Emtricitabine (FTC)

Though FTC is structurally similar to 3TC [34], we were unable to find any studies confirming an association with macrocytosis.

Didanosine (ddI)

Throughout the available literature, ddI does not appear to be associated with macrocytosis. Kahn and colleagues conducted a multicenter, double-blind study involving 913 patients who had tolerated AZT for at least 16 weeks [35]. The median MCV in all subjects at baseline was 110 fl. Out of the 298 subjects who were randomly assigned to ddI, the median MCV decreased to 89 fl, a normal MCV level. Those that remained on AZT sustained an elevated MCV as expected. These findings were supported by Vella and colleagues [36]. They performed an open, randomized, multicenter study to evaluate the clinical benefit of switching from AZT to ddI in HIV-infected patients after 6-18 months of AZT treatment. After 12 months of treatment, subjects that received ddI had a decrease in MCV by 15 fl compared to a stable, elevated MCV in those that continued AZT. The authors did not comment on the baseline MCV prior to ddI initiation.

In the study by Steele et al., four adherent patients had taken ddI alone for greater than 24 weeks and the average percent increase in MCV was not statistically different from zero [17]. Another study identified a non-significant decrease in mean baseline MCV from 90.77 fl to 85.85fl (mean change: -4.91fl) after 90 days of treatment with ddI monotherapy in 11 patients [14]. Two other studies also confirmed that ddI did not increase MCV to levels that were statistically significant [6,15]. Based on the above literature, it can be confirmed that ddI is not associated with macrocytosis.

Tenofovir (TDF)

Few articles have addressed TDF and macrocytosis. Khawcharoenporn and colleagues failed to find an association (p = 0.133), even though TDF is commonly prescribed with 3TC, the only agent they found to be associated with macrocytosis [12]. Bhagat and colleagues reported MCV values as a secondary analysis of their study assessing the effect of ART on hemoglobin A2 values. MCV was within normal limits for all 12 patients on tenofovir-based regimens [30]. Diop et al. similarly found no significant association between macrocytosis and treatment with TDF (p = 0.47) [15]. Based on the available literature, it does not appear that TDF is associated with increased MCV or macrocytosis. This is likely due to its low affinity for cellular DNA polymerases [20].

Abacavir (ABC)

There are only two studies to our knowledge that examine a relationship between ABC use and macrocytosis or MCV values [12,15]. Both failed to find an association between ABC and macrocytosis when assessed individually from other NRTIs. These data suggest that ABC is not associated with macrocytosis.

Discussion

NRTI agents continue to be a recommended component of first-line antiretroviral regimens for treatment-naïve patients [2]. Macrocytosis is a known adverse effect of the older thymidine analog NRTIs, but much less is known about its association with the non-thymidine analog NRTIs. The mechanism for this is unclear, but may be due to non-selective inhibition of mammalian DNA polymerases responsible for erythrocyte formation. A review of the literature confirms that AZT is the NRTI most likely to induce a macrocytosis, and is the only member of the class that has also been associated with macrocytic anemia. This can have clinical implications in resource-constrained areas that still widely prescribe AZT, as macrocytic anemia can be associated with poor clinical outcomes and should be managed appropriately. MCV levels have also been used to assess adherence to AZT, as virtually all patients receiving AZT experience a significant increase in MCV by 8-12 weeks. It has been clearly demonstrated that adherence is a major factor in achieving HIV treatment goals, including virologic suppression, restoration of immunologic function, and extended lifespan. As clinicians continue to struggle to identify sufficient methods for monitoring adherence in HIV-infected patients, they are looking beyond traditional modalities

such as patient interviews, pharmacy refill logs, pill counts, and virologic response. As such, the utility of MCV values as a measure of adherence to these regimens may further help to identify non-compliance and address barriers to medication adherence in these patients.

Limiting the findings of this review, is the fact that the data are complex and difficult to analyze due to the various risk factors for macrocytosis that many HIV-infected patients have, including medication use. Additionally, an underestimation of MCV increase could have occurred due to nonadherence, which is common in certain populations. To date, other classes of antiretrovirals are not known to cause macrocytosis, including the PIs, NNRTIs, and INSTIs.

This report has additional clinical applicability in terms of helping clinicians identify drug-induced causes of macrocytosis in patients on ART. We found that macrocytosis tends to be a benign adverse drug effect when associated with NRTIs given that AZT is the only one of these agents that has published reports of macrocytic anemia. This may save clinicians from an unnecessary and potentially costly work-up of macrocytosis in select patients. Furthermore, clinicians may utilize this information as a modality for measuring adherence in patients on AZT or d4T, as these agents reliably produce an increase in MCV. Fortunately, AZT and d4T-based regimens are no longer commonly used as the NRTI agents of choice, largely due to the development of newer drugs with fewer adverse effects and improved tolerability. For this reason, TDF, FTC, ABC, and 3TC have succeeded AZT and d4T as the preferred NRTI agents to use for most treatment populations. These regimens are less likely to be associated with macrocytosis and therefore may eliminate the relative utility of MCV as a surrogate marker of adherence outside of resource-constrained areas that still commonly use AZT and d4T. Other adherence monitoring techniques and testing modalities may be better markers of adherence for these newer and more common NRTI-based regimens.

Conclusion

NRTIs may be an under-recognized cause of macrocytosis with the advent of newer antiretrovirals with improved toxicity profiles. Of the NRTIs, the thymidine analogs (zidovudine and stavudine) reliably produce an increase in MCV. Zidovudine appears to have the greatest impact on MCV and has also been associated with macrocytic anemia. Macrocytosis has been associated with stavudine as well, but to a lesser extent than zidovudine. There is conflicting, low-quality evidence that suggest lamivudine may be linked to elevated MCV levels, however, most cases could not rule out concomitant zidovudine or stavudine use. There are no published reports to support a link between any of the other NRTIs and macrocytosis.

Acknowledgments

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