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Impact of Antiretroviral Agents on Blood Cell Parameters

Onukak, E.E.[1]*, Onukak, A.E. [2], Akwiwu, E.C.[1], Akpotuzor, J.O.[1]
Department of Haematology and Blood Transfusion Science, University of Calabar, Calabar, Nigeria[1].
Department of Internal Medicine, University of Uyo, Uyo, Nigeria [2].
Author for Correspondence *:emeonukak615@gmail.com/+234-806-151-2321.
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Summary
Human immunodeficiency virus infection continues to be a major public health challenge in under-developed regions due to poverty, war and illiteracy. In developed countries, where much success has been achieved in fighting the menace, access to improved therapy is largely responsible. Nevertheless, studies have linked HIV and antiretroviral therapy with increased risk of cytopenia of all major blood cell lines and associated morbidities such as anaemia and platelet-driven cardiovascular events. Some antiretroviral agents such as zidovudine are associated with bone marrow suppression and an increased risk of developing anaemia. Stavudine, azidothymidine and lamivudine have been linked with macrocytic anaemia in patients taking them. Lamivudine in combination with zidovudine causes neutropenia, anaemia and thrombocytopenia. Nevirapine causes eosinophilia, granulopenia and increased enzyme activities. Abacavir sulphate has been linked with increased risk of platelet-driven cardiovascular complications. The advocacy for combined therapy has helped to curb the effects of these agents when taken individually. Prolonged use of highly active antiretroviral therapy has been shown to correct some of these cytopenias and their associated morbidities. In managing HIV-infected patients however, regular monitoring of their blood cell parameters and $CD4^+$ count is required to ascertain the efficacy of the regimen being used in treatment.

Keywords: Impact, Antiretroviral Agents, Blood Cell Parameters

Introduction
Human immunodeficiency virus (HIV) infection was initially recognized as a global health challenge but has gradually become manageable as any other chronic disease. This has been largely attributed to the ease in accessing continuously improved therapy, although the emergence of a global pandemic such as the outbreak of COVID-19 can prevent People Living With HIV (PLWH) from accessing adequate medical care. Notwithstanding, antiretroviral therapy (ART) has led to dramatic improvements in health so that people living with HIV no longer progress to AIDS. Human immunodeficiency virus (HIV) is associated with numerous abnormalities of red blood cells production and lifespan including anaemia (Adias *et al*., 2006). However, studies have linked both HIV and ART with increased risk of certain blood cell derangements and associated morbidities such as persistent anaemia and platelet driven cardiovascular events, particularly myocardial infarction. In Nigeria, some studies aimed at understanding anaemia in HIV infection have shown impaired iron utilization even in situations when there is excessive iron available (Okafor *et al*., 2016; Sabin *et al*., 2016, Akwiwu *et al*., 2017; Taylor *et al.,* 2019; Akwiwu, *et al*.,2020).

Haematological complications of HIV which include cytopenia of all major cell lines were recognized shortly after the first description of AIDS cases. Anaemia, the most common abnormality that causes chronic fatigue, affects cognitive function and influences the choice of ART and opportunistic infection medications. Neutropenia and thrombocytopenia are often asymptomatic with increasing severity and

prevalence as illness advances to AIDS (Spivak *et al*., 1984; Ellaurie *et al*., 1988; Suarez *et al.,* 1994; Mwanda, 1997; Moore, 1999; Karpatkin *et al*., 2002; Adetifa *et al.*, 2006; Consolini *et al.*, 2007; Kibaru *et al*., 2015; Akwiwu *et al.*, 2021). Suppression of viral load in addition to increased $CD4^+$ cell count following HAART improves the survival rate of HIV-infected patients (Asfaw *et al*., 2015). However, HAART does not completely eliminate the risk of HIV-associated morbidity and mortality. While it is agreed that these risks are generally reduced among infected subjects on HAART, certain individual agents have been implicated concerning derangement of blood cell parameters.

Antiretroviral therapy has greatly altered the course of HIV infection from a global pandemic to a manageable health condition. Apart from arresting viral replication, reversing associated morbidities is of great concern in the management of HIV infection. Unfortunately, some antiretroviral agents have been reported to impact adversely on blood cell parameters. There appears to be varying reports regarding peripheral blood cell parameters following HAART therapy. These conflicting outcomes could be dependent on the HAART drug combination used in the studies. This has necessitated a compilation and analysis of literature on the impact of HAART on blood cell parameters, hence the present review. This study therefore aimed at reviewing the impact of antiretroviral agents on blood cell parameters with a view to highlighting reported HAART agents with significant adverse effects on blood cell parameters.

Method for Literature Search

A narrative literature search was conducted using electronic databases such as PUBMED, Google scholar, Google and Research gate. The searches used the terms 'HAART and haematological parameters'; 'HAART and red blood cells'; 'HAART and white blood cells'; 'HAART and platelets'. Relevant articles with the search terms were identified and included in the study. Additional searches were also made in the reference lists of articles covering the theme.

History of Antiretroviral therapy

Azidothymidine (AZT), later called zidovudine (ZDV), was the first antiretroviral agent approved for treatment of HIV patients in 1987. A nucleoside reverse transcriptase inhibitor, ZDV was observed to confer peak survival at 24 weeks of administration but lacked long-term survival benefits (Fishl *et al*., 1987; St Clair *et al*., 1987; Fishl *et al.,* 1990). This development encouraged the entry of other NRTIs including zalcitabine (ddC), didanosine (ddI) and stavudine (d4T). However, associated adverse effects from these drugs led to administering the drugs sequentially and alternatively, but this approach did not yield encouraging results (Skowron *et al.,* 1993). The next approach taken with somewhat encouraging results was combination NRTI therapy. It was observed that ZDV administered with ddC or ddI yielded better results in terms of CD4+ lymphocyte increase and patient survival, although tolerability remained poor (Delta Coordinating Committee, 1996; Hammer *et al*., 1997). Additionally, lamivudine (3TC) was also introduced. It was associated with increased resistance when administered as a monotherapy, but was synergistic when administered with many of the other nucleosides including ZDV (Kuritzkes *et al*., 1999). In all, a milestone attained with the initial use of NRTIs was the discovery that treatment of pregnant HIV-infected women significantly reduced HIV transmission to the newborn (Connor *et al*., 1994).

The next advancement in antiretroviral therapy was the development of drugs from different classes such as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). The first NNRTI that received approval in 1996 was nevirapine; which when administered as a monotherapy developed resistance quickly, but was very effective when administered in combination with two nucleosides (Montaner et al., 1998). Saquinavir was the first protease inhibitor to be approved in 1995 (Cameron *et al*., 1999). This period birthed the highly active antiretroviral therapy (HAART) era (Hammer *et al*., 1997). Over the past years, new potent and relatively safer antiretroviral drugs belonging to the older classes (NRTI, NNRTI and PI), and new classes

(entry/attachment inhibitors and integrase inhibitors) have been developed (Lalezari *et al.,*2003; Gallant *et al*.,2004; Gallant *et al*., 2006; Cooper *et al*.,2010).

Impact of Antiretroviral Agents on Blood Cell Parameters

Studies had shown that some antiretroviral drugs have cytopenic effect especially when used as monotherapy. This has in part encouraged the switch to combined therapy particularly HAART as currently used. The introduction of HAART has greatly improved the quality of life of persons living with HIV and has reduced the rate of advancement of HIV infection to AIDS (Cohen *et al*., 2011). Drug regimens recommended as first line antiretroviral therapy (ART) for HIV consist of a combination of two nucleotide reverse transcriptase inhibitors (NRTIs), typically either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) and emtricitabine (FTC), or abacavir sulphate (ABC) and lamivudine, plus a third agent such as an integrase inhibitor, non NRTI or protease inhibitor (World Health Organization, 2016; European AIDS Clinical Society, 2017).

Unfortunately, use of the HAART is also associated with some adverse effects. Anaemia, leukocytopenia, neutropenia, thrombocytopenia and depletion of CD4 cells are the common haematological disorders associated with antiretroviral therapy (Dikshit *et al*., 2009). As the advancement perceived by the introduction of HAART is yet to achieve zero cytopenia, reports continue to emerge on the current state of this discourse. A limitation encountered in the course of this review is that not all the studies were able to narrow down their observations to specific HAART type or agent.

Antiretroviral Agents and Red Blood Cell Parameters

Anaemia is the most common haematological abnormality seen in patients with HIV infection. The three main causes of anaemia in HIV are decreased red blood cell production, increased red blood cell destruction and blood loss. Decreased red blood cell production may occur due to infection, use of myelosuppressive drugs, infiltration of the bone marrow by neoplasm, decreased synthesis of endogenous erythropoietin, hypogonadism, HIV infection itself and ineffective response to erythropoietin. Increased red blood cell destruction may occur due to thrombotic thrombocytopenic purpura, red blood cell autoantibodies, glucose-6-phosphate dehydrogenase deficiency, haemophagocytic syndrome, disseminated intravascular coagulation and as a result of use of various medications. Blood loss may occur due to conditions such as neoplastic disease or gastrointestinal lesions following opportunistic cytomegalovirus infection (Phillips and Groër, 2002; Volberding *et al.*, 2004).

When used for longer periods of time, HAART has been associated with greater likelihood of correcting anaemia. A study by Assefa *et al*. (2015) on 1061 HIV-infected persons showed a prevalence of anaemia of 42.9% before ART, 20.9% after 6 months of ART and 14.3% after 1 year of ART (Assefa *et al*.,2015). Gedefaw and Colleagues (2013) found an anaemia prevalence of 23.1% in 234 PLWHA. When these individuals were divided into two groups according to treatment, it was observed that the prevalence of anaemia in the group receiving ART was 16.2% and 29.9% in the group not receiving ART (Gedefaw *et al*., 2013). Mocroft *et al*. (1999) in their study found that, 65.5 % of patients were anaemic before using HAART, 53 % were anaemic after 6 months of taking HAART ($p < 0.0001$), and 46 % were anaemic after 12 months of taking HAART (Mocroft *et al*., 1999). Huang *et al*. (2000) found an increase (although not statistically significant), in haemoglobin concentration, with a mean increase from baseline of 13.9 to 14.1 g/dl after 3 months of treatment. After 6 months of treatment, haemoglobin concentration increased to 14.6 g/dl ($p < 0.01$), 9 months: 14.6 g/dl ($p = 0.001$) and at 12 months, MCHC was 14.3 g/dl ($p < 0.01$) (Huang *et al*., 2000).

Previous report in Nigeria (Ejele *et al*., 2005) that evaluated the effect of HAART (stavudine 40 mg, lamivudine 150mg and nevirapine 200mg) twice daily for twelve weeks on the haematological parameters indicated a decline in

the occurrence of anaemia, neutropenia, thrombocytopenia and leucopenia at baseline from 84.3%, 24.3%, 11.4% and 11.4% to 75.7%, 7.1%, 5.7% and 1.4% respectively after 12 weeks of HAART. This study concluded that that highly active antiretroviral therapy of two reverse transcriptase inhibitors (stavudine and lamivudine) and one non -nucleoside reverse transcriptase inhibitor (nevirapine) may improve cytopenia in HIV-infected Nigerians and may be used in patients with haematologic intolerance to other regimen.

Bolton-Moore *et al*. (2007) carried out a similar study and found that the mean haemoglobin concentration increased from 10.3 g/dl at baseline to 11.3 g/dl (CI 95 % 11.2–11.4 g/dl) after 6 months of HAART (Bolton-Moore *et al*., 2007). In a study by Nacoulma *et al*. (2007), haematological changes after 6 months of AZT based HAART showed anaemia at 51.4 vs 80.3 % at baseline (P = 0.0001). A marked increase was also observed in MCV following treatment with HAART (Nacoulma *et al.,*2007). Huang *et al*. (2000) found an increase of MCV from baseline of 5.5 to 98.9 fl ($p < 0.1$) at 3 months, 105.5 fl ($p < 0.001$) at 6 months, 106 fl ($p < 0.001$) at 9 months and 102.8 fl ($p < 0.001$) at 12 months (Huang *et al*., 2000). Similarly, a study by Kibaru *et al*. (2015) found that at baseline 35.9 % study participants had haemoglobin concentration <10.0 g/dl compared to 16.6 % ($p < 0.001$) after 6 months of ART; while 31% had a mean corpuscular volume (MCV) below the 70 fl compared to 8.3 % ($p < 0.001$) at end of 6 months of ART treatment (Kibaru *et al*., 2015).

A study by Takuva *and co-workers* (2013) showed an anaemia prevalence of 25.8% in 10259 PLWHA in South Africa. After commencing treatment in 322 of these individuals, the percentage of anaemia doubled. The ART regimen used was based on zidovudine (Takuva *et al*., 2013). Zidovudine has been described as a possible inhibitor of erythroid colony-forming units, resulting in decreased red blood cell production. Thus, patients being treated with a zidovudine-based ART regimen are 3.34-fold more likely to develop severe anaemia than patients being treated with a non-zidovudine ART regimen (Parinitha and Kulkarni, 2012; Tamir *et al*., 2018).

Antiretroviral Agents and White Blood Cell Parameters

Most HIV-infected patients develop more than one cytopenia as the disease progresses. One important underlying mechanism is haematosuppression due to destruction of haematopoietic progenitor cells and infection. If this mechanism is at work, normal haematopoiesis may be restored if viral replication is effectively suppressed, given that the progenitor cells are not permanently destroyed (Moses *et al*., 1998; Huang *et al*., 2000). Years after effective treatment with HAART, sustainable suppression of viral load is achieved, leading to a resultant increase in $CD4^+$ cell count. However, the $CD4^+$ cell count before initiation of HAART will determine whether or not the cell count will return to normal levels following treatment; thus, it is necessary to stick to WHO recommendation of commencing HAART therapy in HIV patients with a baseline $CD4^+$ cell count <350 cells/µL (Gras *et al.,* 2006; Moore and Kerully, 2007; WHO, 2010). Suppression of viral load in addition to increased $CD4^+$ cell count following HAART therapy improves the survival rate of HIV-infected patients (Asfaw *et al*., 2015).

There appears to be conflicting reports regarding circulating lymphocytes, total white blood cells and neutrophils following HAART therapy. These conflicting outcomes could be dependent on the HAART drug combination used in the studies. A typical example is a study carried out by Kayode *et al*. (2020) which recorded different outcomes between zidovudine-containing HAART and non-zidovudine containing HAART. Patients treated with non-zidovudine containing HAART had a significant decrease in total white blood cell count and a significant increase in lymphocyte count. Contrarily, patients treated with zidovudine-containing HAART had a significant decrease in lymphocyte count and a significant increase in neutrophil count (Kayode *et al*., 2020). Similarly, Kibaru *et al*. (2015) observed a significant decrease in total white blood cell count from 8.7×10^3 cells/mm^3 at baseline to 6.7×10^3 cells/mm^3 ($P < 0.0001$) after 6 months of

HAART; granulocyte count from 2.8 × 10^3 cells/mm^3 at baseline to 2.0 × 10^3 cells/mm^3 (P < 0.0001) after 6 months of HAART; lymphocyte count from 4.8 × 10^3 cells/mm^3 at baseline to 4.2 × 10^3 cells/mm^3 (P < 0.0001) after 6 months of HAART. In the study by Kibaru *and Co-workers (2015),* 86.9% of the study participants were on zidovudine-containing HAART, 11.3% were on stavudine-containing HAART, and 1.8% were placed on other combinations (Kibaru *et al*., 2015).

Antiretroviral Agents and Platelet Parameters

Thrombocytopenia is thought to be the first haematological manifestation of HIV infection. It is influenced by the $CD4^+$ T lymphocyte count, the age, the presence of HCV/HBV coinfection, the presence of opportunistic infections and ART treatment. Different countries have different prevalences of thrombocytopenia in PLWHA (Vishnu *et al.,2015;* Marchionatti and Parisi, 2021). A study in Cameroon (Nka *et al.,* 2019) reported 19.03% (59/310) prevalence of thrombocytopenia with a predominance of mild thrombocytopenia 17.42% (54/310). In that study, more specific findings included that:

1. The mean blood platelet count was 217.64±77.09 and ranged from 34.000 to 466.000/µL.
2. According to CD4 T lymphocytes, mild thrombocytopenia was 33.33% (17/51) among those with severe immunodeficiency, with a statistically significant difference (p=0.003) as compared to those with higher CD4. Furthermore, a weak positive and significant correlation was found between CD4 count and platelet count, r=0.21.
3. Up to 34.1% (27/79) of thrombocytopenic patients were on viral load>$3\log_{10}$, a significant higher burden as compared to those with low-level viremia, p=0.037. Furthermore, a weak negative correlation was found between platelet count and viral load; r = - 0.12.
4. After adjusting for gender, ART, viral load and CD4, Viral load and ART exposure were significantly associated with decreased risk of thrombocytopenia (p < 0.001).

Apart from the 19.03% thrombocytopenia reported by Nka and co-workers (2019), other studies on prevalence of thrombocytopenia in newly diagnosed HIV infection include; Tene *et al*. (2014) who carried out a study in the same population of Yaoundé Cameroon, and reported a prevalence of 13.67%, Taremwa *et al.* (2015) in southwestern Uganda in 2015, in which 17.4% was obtained, Alaei *et al*. (2000) in Iran in 2000 in which 20% was reported, Kibaru *et al.* (2015) in Kenya in which 20% was observed.

Reports of thrombocytopenia among persons on therapy is shown as follows; Cameroon: 6.9% (Nka *et al*., 2019); Uganda: 13% (Taremwa *et al.,* 2015); Ethiopia: 4.1% (Wondimeneh *et al.*, 2014); Kenya: 6.5% (*Kibaru et al., 2015*). Nka and Co-workers (2019) concluded that thrombocytopenia occurs especially among ART-naïve, AZT-containing regimens, high viremia and severe immune-compromised patients.

In addition, lower platelet counts but higher PDW have been reported in Calabar, Nigeria (Akwiwu *et al.*, 2019). In that report, it was stated that although the finding of lower platelet count could arise from insufficient production as well as increased consumption, the observation of higher PDW value suggests the later. The PDW represents the variability in platelet size and is thought to be an important marker of platelet activation (Farias *et al*., 2010; Vagdatli et al., 2010; Harsha and Chaithra, 2013; Aydogan et al., 2015 and Osime *et al*., 2015).

Implicated Antiretroviral Agents with Adverse Effect on Blood Cell Parameters

Some antiretroviral agents used in treatment of HIV-infected patients are associated with bone marrow suppression and an increased risk of developing anaemia. The drug most implicated is zidovudine, a reverse transcriptase inhibitor. The exact mechanism of anaemia associated with zidovudine therapy is unknown, but it has been hypothesized that the drug may suppress erythropoiesis or inhibit erythroid stem cells, resulting in pure red blood cell aplasia. The defect in red blood cell production may lead to production of fewer but larger cells, thus increasing the mean corpuscular volume. Complications from zidovudine therapy are reversible upon withdrawal of the drug and reduction of dosages (Huang et al., 2000; Balakrishnan *et al*., 2010; Kuwalairat *et al*., 2014).

In a study that enrolled 337 children in Kenya (Kibaru *et al*., 2015), Zidovudine-Lamivudine backbone (AZT/3TC) based regimens were the most frequently used first line ART protocol and used by 291 (86.3 %) children in combination with efavirenz (EFV), nevirapine (NVP) or abacavir (ABC). Stavudine-based combination was the other common protocol. Children with Stavudine combination had higher haemoglobin increments as compared to zidovudine or other combinations. There was statistically significant increase in mean haemoglobin level in both zidovudine and stavudine combinations but the mean haemoglobin change was more with stavudine combinations at 1.83 g/dl for stavudine combination and 0.7 g/dl for zidovudine combinations. Indications of choice of regimen to use were based on baseline haemoglobin levels. Majority of children with haemoglobin of above10 g/dl were started on zidovudine combination while children with low haemoglobin of less than 10 g/dl were started on stavudine or other combinations. Mildvan *et al*. (2007) conducted some studies to analyze the association between the 16 most frequent combinations of ART and the presence of anaemia. Results showed that the regimens associated with the global prevalence of anaemia were abacavir/ZDV/lamivudine, ZDV/ lamivudine/indinavir and ZDV/lamivudine/ efavirenz. In constrast, a low prevalence of anaemia was observed in subjects receiving didanosine/stavudine/efavirenz, didanosine/ stavudine/nelfinavir and stavudine/lamivudine/ indinavir. Summarily, all ZDV-containing regimens were associated with an increased risk of anaemia, except for the ZDV/lamivudine/ saquinavir regimen.

Haemolysis arising from possible development of autoantibodies to the antiretroviral agents has also been postulated as a mechanism for anaemia in HIV infection but not much literature exists on specific agents with the adverse effect of haemolysis. Features of increased cell volume, mean cell haemoglobin and size variability have been noted among subjects on treatment. This is in addition to the general indices for anaemia namely: reduced haematocrit and haemoglobin concentration. The finding of macrocytic anaemia in HIV infection is mainly seen among those on treatment, and agents such as stavudine, azidothymidine and lamivudine have been implicated, thus reflecting some degree of treatment-associated interference in the normal production of red cells (Richman *et al*., 1987; Snower and Weil, 1993; Eyer-Silva *et al*., 2001; Moore and Forney, 2002; Bozzi *et al*., 2004 ; Khawcharoenporn *et al*., 2007; Kallianpur *et al*.,2016; Panwar *et al*., 2016). Lately, antiretroviral therapy has been considered to be a contributing factor to inflammation in HIV infection and increased anisocytosis as shown by increased red cell distribution width among those on treatment has been reported to align with some markers of cardiovascular risk (Al-Kindi *et al*., 2017).

Adverse effects of lamivudine in combination with zidovudine cause neutropenia, anaemia, thrombocytopenia, and sometimes transient rise in liver enzymes and serum amylase (EMA, 2015; Gebremedhin *et al*., 2019) adverse effects of nevirapine include eosinophilia, granulopenia, jaundice and increased enzymes, while stavudine has been reported to cause anaemia, neutropenia and thrombocytopenia (Swati *et al*., 2016; Zerihun *et al*., 2019).

Indeed, HIV treatment has led to dramatic improvements in health so that people living with HIV (PLWH) no longer progress to AIDS. The major cause of death in PLWH has, however, been reported to be cardiovascular disease (Friis-Moller *et al.,* 2003; Sabin *et al*., 2008; Islam *et al*., 2012). Several studies, however, have linked both HIV and ART with increased risk of platelet driven cardiovascular events, principally myocardiac infarction (Sabin *et al*., 2016; Akwiwu *et al*., 2019; Friis- Moller et al., 2003; Pollack and Rind, 2007; Satchell *et al*., 2010; Satchell *et al*., 2011).

It had been suggested that abacavir sulphate (ABC) may be specifically associated with increased cardiovascular risk. Taylor *et al.* (2019) in their study observed that ABC can pharmacologically alter platelet function in vitro and in vivo. Their study design utilized human HIV negative donors, comparative drug analysis in platelets from a single donor and inbred mice,

meaning that the only variable between experimental groups was drug exposure and that effects reported here can reasonably be attributed to ABC. Their finding thus confirmed earlier epidemiological and clinical observations linking ABC with increased incidence of platelet driven cardiovascular events such as myocardiac infarction (Friis- Moller *et al*.,2003; Sabin et al., 2008; Islam *et al*., 2012).

Conclusion

Varying proportions of uncorrected cytopenia despite HAART administration seem to persist. The conflict in the outcomes of studies focused on impact of HAART on blood cell parameters could be dependent on the HAART drug combination used in the studies. It is thus logically safe to say that the advancement in the treatment of HIV infection from the era of monotherapy to the present time of combined therapy, has not eliminated the adverse effects of the individual agents on blood cell parameters. At best, combined therapy could have reduced such impact though. The drug most implicated with the risk of anaemia is zidovudine, a reverse transcriptase inhibitor. It has been hypothesized that the drug may suppress erythropoiesis or inhibit erythroid stem cells, resulting in pure red blood cell aplasia. The defect in red blood cell production may lead to production of fewer but larger cells, thus increasing the mean corpuscular volume. Complications associated with zidovudine therapy are reversible upon withdrawal of the drug and reduction of dosages.

Literature also has it that adverse effects of lamivudine in combination with zidovudine cause neutropenia, anaemia, thrombocytopenia, and sometimes transient rise in liver enzymes and serum amylase. Reported adverse effects of nevirapine include eosinophilia, granulopenia, jaundice and increased enzymes, while stavudine has been reported to cause anaemia, neutropenia and thrombocytopenia. In addition, epidemiological and clinical observations have linked abacavir with increased incidence of platelet driven cardiovascular events such as myocardial infarction arising from the drug's pharmacological alteration of platelet function.

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