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Abstract

Purpose of review: This review focuses on current studies addressing the association of abacavir (ABC) therapy and myocardial risk in HIV-infected patients, discusses potential pathogenetic mechanisms, and suggests a preliminary algorithm for decision making regarding ABC therapy in daily clinical practise.

Recent findings: The D:A:D study was the first to reveal an increased rate of myocardial infarction in patients recently treated with ABC. Subsequent analyses of both cohort studies as well as prospective randomized clinical trials largely confirmed this association. Although these studies varied considerably by design and their ability to control for confounders, they provide early support that ABC therapy can increase the risk for cardiovascular disease. The pathogenesis of this association remains elusive. Preliminary cross-sectional studies suggest the involvement of inflammation associated to ABC.

Summary: Prospective studies are required to provide additional evidence for the association of ABC therapy and cardiovascular events. In individual patients with underlying high cardiovascular risk, replacement of ABC may be considered, if it can be substituted by alternative equally effective treatment.

Keywords: Abacavir, myocardial infarction, HIV-infection, cardiovascular risk

Introduction:

HIV-infected patients have an excess cardiovascular risk to which traditional risk factors including smoking, diabetes, and aging importantly contribute [1]. These factors can occur in combination with therapy-associated dyslipidemia or HIV-induced immune activation, which both may further aggravate the risk of cardiovascular disease. Cumulative exposure to protease inhibitors contributes to an increased rate of myocardial infarction in HIV-patients, which can partially but not fully be explained by dyslipidemia associated with these drugs [2]. Recent data from the D:A:D study, a large international observational cohort study of HIV-infected patients, suggested an increased risk for myocardial infarction in patients being treated with ABC or exposed to this drug within the preceding six months [3]. These findings were confirmed by several but not all subsequent studies addressing this issue. The pathogenetic mechanism by which ABC contributes to cardiovascular events remains obscure. Several preliminary studies, but not all, are consistent with the view that ABC treatment may promote systemic inflammation in some patients, as indicated by an increase in inflammatory markers. This could potentially contribute to atherosclerotic plaque instability and rupture. In this review, we will summarize the data regarding the association of ABC with cardiovascular disease, consider potential underlying mechanisms and discuss the implications of these findings for the clinical care of patients with HIV.

ABC use and coronary vascular events in observational and randomized clinical studies

In 2008, the D:A:D Study Group [3] was the first to describe an association of current or recent (within the last six months) ABC use and an increased rate of myocardial infarction. D:A:D is an international collaboration of 11 cohorts, following 33,347 HIV-infected individuals from Europe, the USA, and Australia. Patients were on active follow-up in their

cohort at the time of enrolment into D:A:D (December 1999 to January 2005). During 157,912 person-years of follow up 517 patients have been reported with a confirmed myocardial infarction. Current/recent, but not cumulative use of ABC was associated with an increased rate of myocardial infarction (compared to those with no recent use of the drugs, relative rate 1.90, 95%CI 1.47-2.45 [p=0.0001]). Rates were no longer significantly increased after abacavir had been discontinued for longer than six months. After adjustment for the predicted 10-year risk of coronary heart disease, recent use of ABC remained associated with increased rates of myocardial infarction and was most evident in patients with a high predicted underlying cardiovascular risk, as determined by the Framingham risk score. Although channelling bias, an effect observed due to the preferential prescription of ABC to persons perceived to be at risk of cardiovascular disease, could have influenced these results, several factors suggest this to be an unlikely explanation. First, the risk of ABC was not reduced by adjustment for known coronary vascular disease risk factors including those known to be possibly affected by antiretroviral therapy. Second, the risk was no longer present after discontinuation of ABC. Third, the risk of ABC was specific for myocardial infarction and other outcomes related to coronary artery disease. Interestingly, there was no association with stroke, which shares many risk factors with myocardial infarction and in part would have been expected to be affected by the same bias. Finally, follow up data from D:A:D later showed [4] that the same effect was not observed with tenofovir, another drug preferentially prescribed to avoid metabolic complications, which would have been expected to be associated with a similar potential channelling bias.

Subsequent analysis of data from the Strategies for Management of Anti-Retroviral Therapy (SMART) study [5], a randomized study to compare continuous therapy with CD4 cell-guided treatment interruption, confirmed that current use of ABC was associated with an excess risk of cardiovascular disease as compared to other NRTIs. One needs to consider, however, that

the power of this analysis was more limited given the smaller event rates. Adjusted hazard ratios for predefined outcomes including clinical myocardial infarction (n = 19), major CVD (myocardial infarction, stroke, surgery for coronary artery disease, and CVD death; n = 70), expanded CVD (major CVD plus congestive heart failure, peripheral vascular disease, coronary artery disease requiring drug treatment, and unwitnessed deaths; n = 112) in the continuous therapy arm for ABC versus other NRTI were 4.3 [95% CI: 1.4-13.0], 1.8 (1.0-3.1), and 1.9 (1.3-2.9), respectively. Analysis of baseline biomarker data available in a subset of patients revealed that high sensitivity-C-reactive protein and interleukin-6 were 27% (p = 0.02) and 16% (p = 0.02) higher for patients receiving ABC (N = 175) compared to those receiving other NRTIs (n = 500).

Prompted by these two studies, ABC's manufacturer presented compiled HIV clinical trial safety data from GlaxoSmithKline-sponsored clinical trials, of which 12 were randomized studies [6]. In 14,174 HIV-infected adults who received ABC (n = 9,502; 7,641 person-years) or not (n = 4,672; 4,267 person-years) myocardial infarction rates were comparable among subjects exposed [n = 16 (0.168%; CI: 0.096 to 0.273; 2.09 per 1000 person-years)] or not exposed [n = 11 (0.235%; CI: 0.118 to 0.421; 2.57 per 1000 person-years)] to ABC-containing therapy. Thus, this pooled summary with few myocardial infarction events did not find an excess risk of myocardial infarction with ABC therapy. Similarly, a combined analysis of 3,207 patients randomized to first antiretroviral therapy as part of five ACTG trials (781 randomized to ABC) identified 24 myocardial infarctions and 56 severe vascular events, but no association of ABC use and such events [7].

More recent data originated from the French Hospital Database on HIV. Using a nested case-control study, this HIV-cohort study again suggested that recent ABC treatment was associated with increased cardiovascular risk. Cases, enrolled in the database between January 2000 and December 2006, were defined as having a first prospectively reported definite or

probable myocardial infarction after validation using the European Society of Cardiology definition. Overall 286 cases and 865 controls were included in the analysis and 76% of the enrolled patients were therapy-naive. There was evidence of an association between recent exposure to ABC and an increased risk of myocardial infarction, but the risk was limited to the first year of exposure to ABC and no longer significant thereafter (OR=2.19, 95% CI: 1.19-4.02) [8]. Recently, additional retrospective analyses from insurance data sets such as the Quebec's public health insurance database (QPHID) [9] or the Veterans Adminstration's Clinical Case Registry [10] were presented at the 2009 International AIDS Society Pathogenesis and Treatment Conference. The QPHID again identified an association of myocardial infarctions with ABC [OR 1.74 (95%CI 1.18-2.56)]. The Veterans database reported that the cumulative exposure to ABC was associated with a modest, non-statistically significant increase in acute myocardial infarction, which was further weakened after adjusting for traditional cardiovascular risk factors. This study identified chronic kidney dysfunction as defined by an estimated glomerular filtration rate (eGFR) <60ml/min, a known CVD risk factor in the general population, to be more prevalent in patients receiving ABC. Given that this observation could be consistent with a channelling bias and that chronic kidney dysfunction was not considered in most of the studies indicating the association of ABC with myocardial infarction, this factor should be considered in future studies. A preliminary analysis of available eGFR data in D:A:D did not provide support for chronic kidney disease being an explanation for the findings concerning CVD risk with ABC [11].

Finally, the STEAL study, a randomized simplification study, in which treatment-experienced patients with viral suppression to below 50 copies/mL were switched to simplify their regimen with either fixed-dose ABC+3TC (n=179) or TDF+FTC (n=178) again reported a potential association of ABC with coronary vascular disease. Eight versus one patient in the ABC+3TC and TDF+FTC trial arms, respectively, developed cardiovascular events. This

resulted in a statistically significant difference (p=0.045), although the sample size and the low number of events in this randomized trial limits firm conclusions [12].

Taken together, five of eight studies provide evidence for an association between ABC use and increased cardiovascular risk (Table). Most of these studies, although observational by design, collected data prospectively using predefined clinical end points, and two of them included by far the largest number of cardiovascular events, which underlines their statistical power. Interestingly, patients enrolled in several studies demonstrating an effect of ABC on average were seven to ten years older than patients in the studies not finding an effect. This leads us to speculate that it might be more difficult to detect the association between ABC and CVD in a population of younger individuals considering the overall importance of age as an independent cardiovascular risk factor.

Atherosclerotic plaque formation, growth and rupture

One of the first steps in the process of atherosclerotic plaque formation is endothelial activation, characterised by increased surface expression of adhesion molecules such as VCAM-1 [13]. This contributes to platelet adhesion and monocyte infiltration, the latter of which differentiate into macrophages, convert into lipid laden foam cells and produce inflammatory cytokines thereby further aggravating endothelial activation. Over time this results in atherosclerotic plaque formation and growth. This cascade is paralleled by recruitment of lymphocytes including CD4+ T cells, which also promote endothelial activation, plaque formation and growth through release of cytokines such as IFNγ, which reduces collagen synthesis by vascular smooth muscle cells (vSMC). Other mediators such as IL-1 and TNFα increase release of matrix metalloproteinases (MMP) by macrophages, endothelial cells, and vSMC leading to breakdown of collagen and plaque extracellular matrix

[14]. This process is further promoted by the release of serine proteases from activated mast cells within the atherosclerotic lesion and can result in plaque instability and eventually plaque rupture. Rupture of a plaque or erosion of the endothelium, leading to exposure of thrombogenic material, represents the primary trigger of arterial thrombosis mediated by tissue factor release [15]. The latter is sustained by CD40 stimulation on macrophages through CD4+ T cells and proinflammatory cytokines such as IL-1 and TNFα. Platelets are rapidly recruited to the site of rupture with subsequent platelet activation and aggregation by PAI-1, which is released by endothelial cells and vSMC. Concomitantly, the coagulation cascade including the generation of fibrin (the main protein component of the thrombus) is activated. Blood exposure to tissue factor, a protein present in the atherosclerotic plaques, initiates the cascade. It is believed that the high circulating levels of tissue factor in patients with CVD might also contribute to thrombosis after plaque rupture [16]. If the thrombus blocks the artery this may result in myocardial infarction.

Interestingly, patients receiving ABC in the SMART study at recruitment had more than 25% increased high sensitive CRP (hsCRP) levels and about 15% higher systemic IL-6 concentrations, as compared to patients treated with other NRTI, although the absolute differences were limited [17]. In contrast, the HEAT study reported that treatment-naive patients treated with ritonavir-boosted lopinavir either with ABC+3TC or TDF+FTC showed similar reduction in endothelial activation markers such as soluble VCAM-1, IL-6, and hsCRP [18,19]. Although not confirmed by all [20], the current data would be consistent with the view that HIV infection is a cardiovascular risk factor [21], as it causes an inflammatory status with increased expression of VCAM-1, high levels of hsCRP, IL-6, and TNFα and hypercoagulabiltiy by increased d-dimer and PAI-1 levels. Virus suppression through antiretroviral therapy either with or without ABC commonly results in improvement of many of these alterations [22,23], although exceptions have been reported [24]. This could be

different in a situation where an effectively treated patient introduces ABC as a new component of the regimen, resulting in small but significant increase of inflammatory mediators such as CRP and IL-6 [17], reduced fibrinolytic capacity due to raised PAI-1 levels [25], or increased circulating MMP-9 concentrations [26]. Interestingly, almost all of the above mentioned studies that demonstrated the association between ABC and myocardial infarction considered patients with low or undetectable viral load, in contrast to the studies failing to show such an association. It can be speculated that low level viremia, by causing mild inflammation, is a contributing factor for the effect of ABC on the increased rate of cardiovascular events. Other observations support the possible involvement of an inflammatory component. Despite the close HLA-B57 association in many cohorts [27] and the conclusive elucidation of the CD8 T cell response contributing to the ABC hyperpsensitivity reaction [28], a relevant number of HLA-B57 negative patients develop signs and symptoms of hypersensitivity and systemic inflammation. This could be due to other genetic risk factors (e.g. cross-reacting haplotypes, heat shock protein polymorphisms) or uncharacterised CD4 T cell responses. Thus, more HLA-B57 negative patients may develop mild or even subclinical inflammatory responses that only rarely develop to clinically equivalent of the hypersensitivity observed in HLA-B57 positive patients. Finally, an acute change in the inflammatory status would also be consistent with the observed immediate effect following ABC therapy initiation and the reversibility after cessation. In addition, preliminary data showing a reduced endothelial function among patients receiving ABC with undetectable viremia [29] and increased platelet aggregation due to hyper-reactive platelets in patients treated with ABC [30] may be suggestive of a low level inflammation and hypercoagulability in patients receiving ABC with detectable viremia (Figure 1). In contrast, other factors such as HIV-infection, gender, smoking, hyperlipidemia and therapy using protease inhibitors contribute to a much slower increase in cardiovascular risk due to cumulative exposure and primarily an impact on atheroma formation and growth.

Clinical implications

The major aim of any antiretroviral therapy regimen is to effectively suppress viral replication to below the detection limit of commercial assays. This should be the mandatory target for all treatment strategies when initiating or changing antiviral therapy. Whether or not ABC constitutes a cardiovascular risk factor equally for patients first commencing antiretroviral therapy and those who are treatment-experienced remains unclear. Given that patients with high underlying cardiovascular risk in terms of absolute risk would be most affected by the observed association between myocardial infarction and ABC therapy, these patients should be particularly considered for cardiovascular risk reduction and therapy modification if applicable. It is imperative to first identify and manage modifiable risk factors such as smoking, arterial hypertension, dyslipidemia, and drug abuse, particularly in ABC-treated patients with a high or moderate underlying cardiovascular risk (Table 2). In addition, replacement of ABC or change of the antiretroviral regimen might be considered for these patients, if other drugs or combinations are available to effectively maintain viral suppression. In patients with low cardiovascular risk, modifiable risk factors should be improved but change of antiretroviral therapy seems to be less compulsory.

Conclusion:

Large cohort studies with adequate follow up of large numbers of patients are indispensable for generating sufficient power to identify serious adverse events which occur at relatively low frequency in HIV-therapy. However, by virtue of their design (e.g. non-randomized, non-controlled, non-proportional representation of specific patient groups) and the presence of unknown confounding factors (e.g. channelling bias) they limit definite conclusions.

Nevertheless, these studies are very relevant for generating hypotheses for further validation in prospective clinical and experimental studies. Consequently, this also applies to the reported association between ABC and cardiovascular risk, although, as outlined above, the existing evidence may affect therapeutic decisions in individual patients.

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Table. Cohort studies and clinical trials assessing the association of ABC therapy and the risk for myocardial infarctions. Randomised controlled trial, RCT; myocardial infarction, MI.

Figure 1. Disease- and therapy-associated factors contributing to cardiovascular disease in HIV-infected patients. Myocardial infarction is a result of plaque rupture and hypercoagulation and the deleterious clinical outcome of atheroma formation and growth. All these conditions are facilitated by systemic inflammation. Most of the classical cardiovascular risk factors contribute mainly to atheroma formation and growth via a rather cumulative effect over time. HIV-therapy, specifically therapy with specific protease inhibitors, may negatively affect single feature such as lipids, glucose homeostasis and visceral obesity. HIV-infection and HIV-therapy may exacerbate factors, such as atheroma formation, plaque instability and hypercoagulation, as well as promoting inflammation, which facilitates the overall atherosclerotic processes. Preliminary clinical and experimental data would be consistent with the view that ABC-therapy may contribute to the systemic inflammation (1), may directly cause plaque instability (2) or lead to platelet activation and clotting (3).

Figure 2. Proposed algorithm for the use of ABC in HIV-infected patients. In all patients with HIV the main goal of therapy remains to achieve or maintain maximal viral suppression. In patients with moderate to high underlying cardiovascular risk (e.g. Framingham risk score >10-20%), who receive ABC, modifiable risk factors should be addressed. Replacement of ABC may be considered, but only if possible without jeopardizing virologic suppression *(grey)*. In all other patients, managing modifiable risk factors is recommended, but replacement of ABC appears to be less compulsory.

Table

Study	Design	Event Ascertainment	Patients (n=)	MI (n=)	Abacavir-effect?
D:A:D [3]	Prospective observ. cohort	Prospective predefined	33,347	580	Yes
FHDB [8]	Case control in observ. cohort	Prospective, MI retrospectively validated	289 cases 884 control	289	Yes, first year of exposure
SMART [5]	RCT, Oberserv. analysis	Prospective predefined	2,752	19	Yes
STEAL [12]	RTC	Prospective	357	3	Yes
QPHID [9]	Case control in observ. cohort	ICD 9 code acute MI Not validated	142 cases 1,420 controls	142	Yes
GSK Analysis [6]	RCT (n=54)	Retrospective Data base search	14,174	11	No
ALLRT ACTG [7]	Long term follow up of 5 RCT	Retrospective 2 independent reviewer	3,205	27	No
VACCR [10]	Retrospective Observ. Cohort	ICD 9 code acute MI Not validated	19,424	278	No

Figure 1

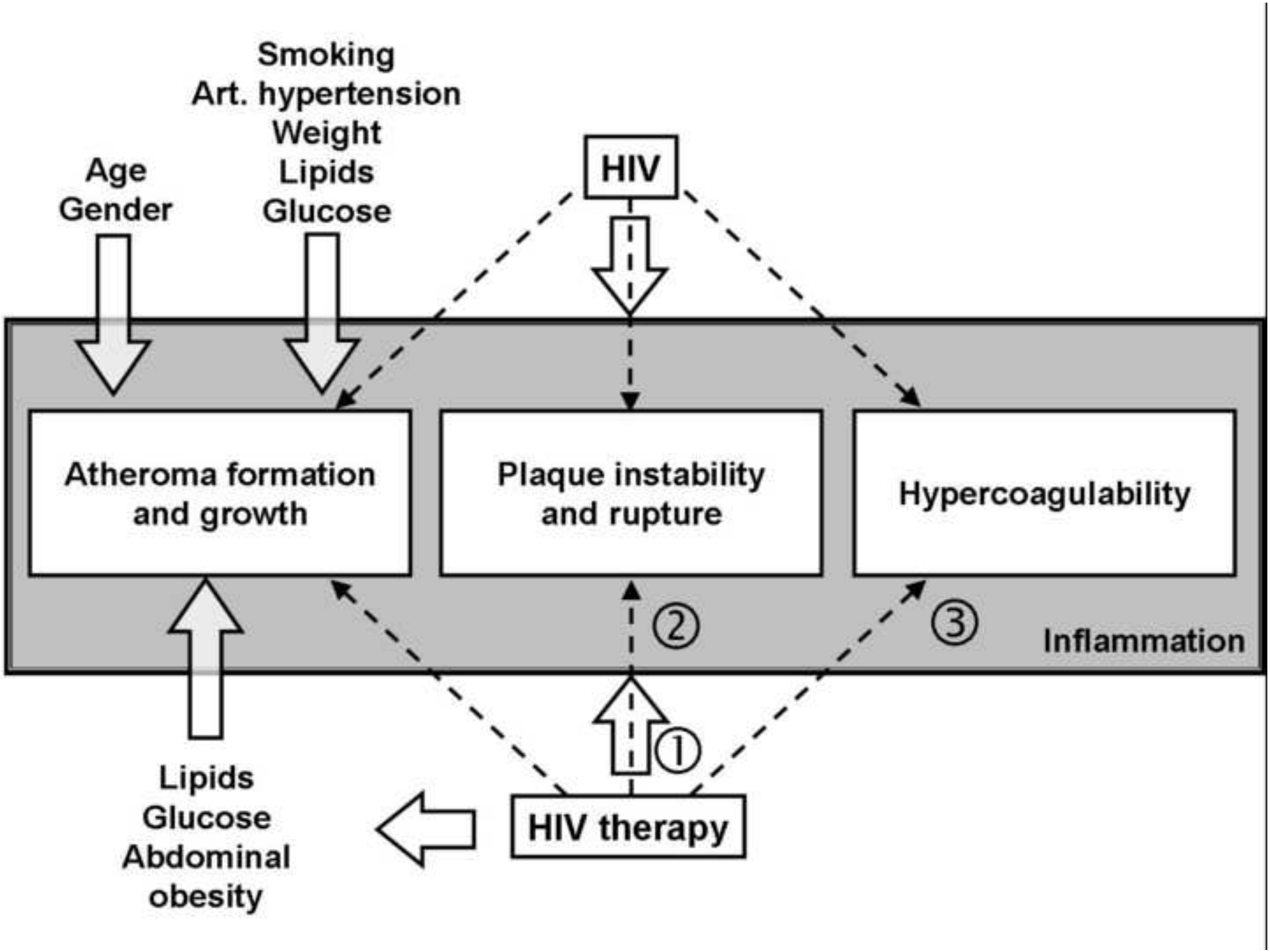
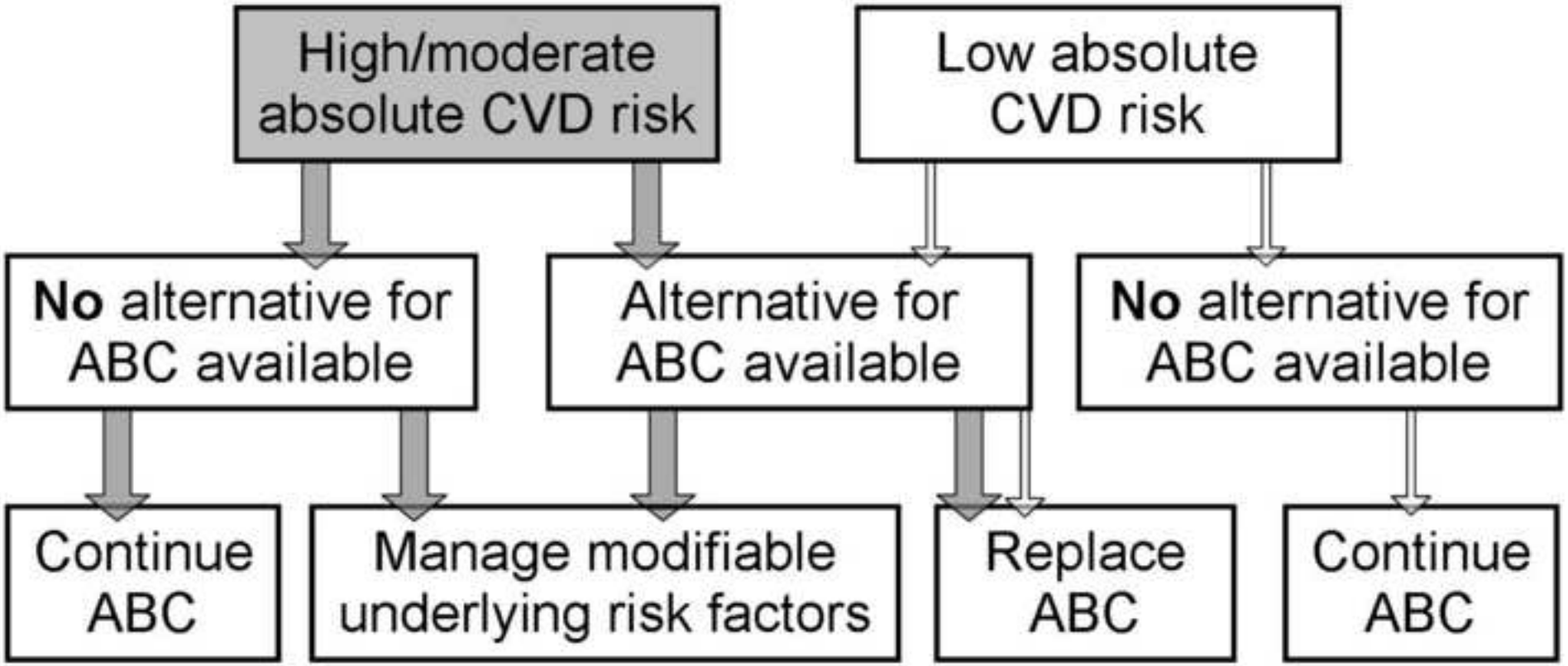

Smoking
Art. hypertension
Weight
Lipids
Glucose
Age
Gender
HIV
Atheroma formation and growth
Plaque instability and rupture
Hypercoagulability
Inflammation
②
③
①
Lipids
Glucose
Abdominal obesity
HIV therapy

Figure 2


High/moderate absolute CVD risk
Low absolute CVD risk
No alternative for ABC available
Alternative for ABC available
No alternative for ABC available
Continue ABC
Manage modifiable underlying risk factors
Replace ABC
Continue ABC