Abacavir and cardiovascular disease: A critical look at the data

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A B S T R A C T

Most HIV-infected subjects will receive a treatment regimen including abacavir or tenofovir. Therefore, clarifying if there is an increased risk of acute myocardial infarction (AMI) among those exposed to abacavir is of the utmost importance. Due to the low frequency of AMI in this young population (2–5 per 1000 patients/year), efforts to clarify this have been quite controversial. While some observational cohorts have found a statistically significant association, others have not. Meta-analysis of randomized clinical trials offering the highest scientific evidence found no association at all, but with a limited statistical power to definitely rule out a small effect. A channelling or selection bias has been demonstrated in cohort studies, favouring the prescription of abacavir to subjects with or at risk for chronic kidney disease, and therefore, with an intrinsic increased cardiovascular risk. The recent NA-ACCORD cohort study does not identify an increased risk for AMI associated with recent abacavir use in a fully adjusted model (HR 1.33; 95%CI: 0.96, 1.88). However, it does find an association in a second analysis restricted to treatment-naïve persons, with higher differences in baseline characteristics among compared arms. A critical review of the compiled available evidence is therefore mandatory, particularly in light of the first single-tablet regimen to receive approval that does contain abacavir.

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Correlation does not equal causation.

Sir Austin Bradford Hill FRS (1897–1991)

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didanosine, with conflicting findings with regard to abacavir (Sabin et al., 2008; Bavinger et al., 2013). There is a general agreement in all analyses that neither cumulative nor past exposure to abacavir seemed to increase the risk of these events, but the potential risk of a recent/current exposure to abacavir remains open to debate.

1. Introduction

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study unexpectedly found an association between recent—but neither cumulative nor past—exposure to abacavir (defined as current exposure or use within the previous 6 months) and increased rates of acute myocardial infarction (AMI; HR 1.89; 95% CI: 1.47, 2.45), and the excess risk disappeared beyond 6 months after drug cessation (Sabin et al., 2008). In relative terms, the effect of recent exposure of abacavir in D:A:D was stronger in those with lower underlying 10-year CVD risk (×2.9 increase, vs ×2.0 in those with high CVD), although the absolute difference was obviously greater in those with higher CVD (from 1.0 to 2–9 events per 1000 person-years in those with low risk, vs 15.9 to 32.5 in those with high risk). The D:A:D investigators have reported that there had been some channelling of abacavir away from those at higher risk of CVD since 2008 in their cohort, but despite this, they continue to observe a strong association between current abacavir exposure and AMI risk in more recent calendar years (Sabin et al., 2016a). They have also analysed the risk of a subsequent MI in persons who have already experienced an AMI (Sabin et al., 2016b). Neither cumulative exposure to abacavir nor the receipt of abacavir at initial AMI were significantly associated with recurrent MI.

Other cohorts (AIDS Clinical Trial Group [ACTG] A5001/ACTG Longitudinal Linked Randomized Trials [ALLRT], French Hospital Database on HIV [FHDH], US Veterans, Boston Hospitals) did not find a significant association (Table 1) (Ribaudo et al., 2011; Bedimo et al., 2011; Lang et al., 2010; Triant et al., 2010).

Of interest, investigators from the US Veterans cohort have reported so far three different analyses showing either no association between recent abacavir exposure and AMI (and even a lower risk of cerebrovascular accidents as well [HR, 0.60; 95% CI: 0.45, 0.79]), or alternatively a statistically significantly association with cardiovascular events (OR = 1.50; 95% CI: 1.26, 1.79) (Table 1) (Bedimo et al., 2011; Desai et al., 2015; Choi et al., 2011). The differing results from these analyses done in the same cohort increase the confusion many physicians have in this issue and their mistrust in observational cohort analyses.

The Kaiser Permanente cohort has shown an association of cumulative abacavir exposure and any CVD in the intention-to-treat analysis (HR 2.2, 95% CI: 1.43, 3.5) but not in the per-protocol analysis (HR 2.1, 95% CI: 0.95, 5.0; p = 0.11) (Marcus et al., 2016).

Of note, both the ACTG A5001/ALLRT and the US Veterans cohorts found no association between cumulative or current abacavir exposure and AMI or cardiovascular events (CVE) even in their unadjusted analysis, despite tenofovir-containing regimens having the lowest HR of AMI in the later (Bedimo et al., 2011). However, their paramount contribution to all this research was identifying that abacavir exposure was more common than was tenofovir exposure among patients with prior chronic kidney disease, and chronic kidney disease independently predicted higher rates of AMI and CVE (Bedimo et al., 2011; George et al., 2010). Common diseases causing chronic kidney disease, like hypertension or diabetes, have an intrinsically high CVD, and those individuals were preferentially prescribed a non-tenofovir treatment, namely abacavir. This is known as a prescription bias and has been identified as a main drawback of non-randomized cohort analysis.

1.1. Data coming from recent cohort analysis

The recent NA-ACCORD and Swiss cohort analyses have reignited the debate of the potential association between abacavir exposure and AMI (Palella et al., 2015; Young et al., 2015).

The first one compares subjects with recent abacavir exposure, defined as prescription within the prior 6 months, versus those starting a non-abacavir regimen. Statistical significance was not given, but there are differences between the two study arms in many baseline characteristics, some of them known to be strongly associated with CVR by their own. Abacavir initiators were more likely to be black, intravenous drug users, to have hepatitis C co-infection, hypertension, renal impairment, high total cholesterol, a CD4 T-cell count <200 cells/μL, and a history of clinical AIDS. This drawback is inherent to observational analyses that lack a random allocation of a drug in exactly the same group of individuals, and therefore are not necessarily the preferred tool to assess potential associations between drug exposure and non-cumulative (short/medium term) adverse events. The investigators use marginal structural models to control for this time-dependent confounding. Despite being a sophisticated statistical technique, there is no certainty that it will succeed in adjusting for the reported channelling bias existing in the cohort, mainly due to missing variables with potential impact on the final event.

The investigators reproduced the analysis as done in the initial D:A:D cohort study (Sabin et al., 2008), and found similar results, with an adjusted HR of 1.71 (95% CI: 1.11, 2.64) for AMI in those receiving abacavir.

The NA-ACCORD investigators then repeated their analysis in the full study population but adjusting also for hypertension, diabetes, renal impairment, high total cholesterol, high triglycerides, and statin use, as suggested by findings of the Veterans Health Administration study (Bedimo et al., 2011). This second analysis did not achieve statistical significance for any increased risk for AMI associated with recent abacavir exposure: HR 1.33 (95% CI: 0.96, 1.88). In a final third sensitivity analysis done only in a subset of treatment-naïve subjects in the cohort, they find a significantly increased risk among those receiving abacavir: HR 1.95 (95% CI not given but excluding 0). Their population was reduced in this subset from 16,733 to 6485 individuals, and incident AMI events decayed from 301 to 93. However, differences in baseline characteristics between abacavir and non-abacavir initiators are numerically higher in this subset of naïves than in their whole cohort. Naïve abacavir initiators were more likely to be black, intravenous drug users, have hepatitis C co-infection, diabetes mellitus, high total cholesterol, hypertension, renal impairment, age, percentage with CD4 T-cell count <200 cells/μL, prior AIDS diagnosis, and ever cigarette smoking, all of them increasing the CVR in the abacavir group.

A limitation of most studies is establishing a compiled “non-abacavir” group that includes many different options, which might have a different impact on CVR. Certainly, the analysis of higher clinical interest would have relied on abacavir versus tenofovir, which is the relevant daily clinical question. Studies in this field have not consistently analysed the association of tenofovir fumarate (the alternative drug most physicians would use instead) with AMI using the same methodology and cohort. This becomes a pivotal issue that may have biased the estimation of treatment effects in these analyses, because abacavir was considered an attractive option by many physicians have in this issue and their mistrust in observational cohort analyses.
Table 1
Main findings of pivotal cohort and case-control nested studies assessing the potential association between abacavir exposure and acute myocardial infarction in HIV-1 infected individuals.

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of analysis</th>
<th>Subjects included</th>
<th>Subjects exposed to ABC</th>
<th>AMI events to ABC analysed</th>
<th>HR for ABC use (95% CI)</th>
<th>AMI events/ p/y</th>
<th>Additional analysis done</th>
<th>Era</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMART (Use of nucleoside reverse, 2008)</td>
<td>Randomized trial, but ABC allocation not randomized</td>
<td>4544</td>
<td>1019</td>
<td>19</td>
<td>Current use</td>
<td>4.25 (1.39–13.0)</td>
<td>4.2/1000</td>
<td>Major CVE also associated with ABC current use (1.80 [1.04–3.11])</td>
</tr>
<tr>
<td>D:A:D (Sabin et al., 2008)</td>
<td>Prospective observational cohort</td>
<td>33,347</td>
<td>–</td>
<td>517</td>
<td>Any. Recent use (current use or use within the previous 6 months)</td>
<td>1.89 (1.47–2.45)</td>
<td>3.3/1000</td>
<td>Cumulative exposure: 1:14 (1.08–1.21); past exposure (last use &gt;6 months previously) 1.29 (0.94–1.77)</td>
</tr>
<tr>
<td>D:A:D (Sabin et al., 2016a)</td>
<td>Prospective observational cohort</td>
<td>4904</td>
<td>–</td>
<td>102</td>
<td>Current use</td>
<td>1.97 (1.43–2.72)</td>
<td>2.6/1000</td>
<td>Results unchanged after stratifying by Framingham risk, and adjusting for renal function, dyslipidemia and hypertension.</td>
</tr>
<tr>
<td>D:A:D (Sabin et al., 2016b)</td>
<td>Prospective observational cohort</td>
<td>816</td>
<td>415c</td>
<td>102</td>
<td>Current use</td>
<td>1.19 (0.79, 1.79)</td>
<td>–</td>
<td>Cumulative exposure to ABC or receipt of ABC at initial AMI not associated with recurrent AMI.</td>
</tr>
<tr>
<td>French Hospital and ANRS cohort (Lang et al., 2010)</td>
<td>Case-control study nested with the ANRS cohort</td>
<td>74,958</td>
<td>410</td>
<td>289</td>
<td>Short-term/recent and cumulative exposure</td>
<td>1.27 (0.64–2.49)</td>
<td>1.2/1000</td>
<td>No association with cumulative ABC exposure (0.88 [0.74–1.04]) or past exposure (1.60 [0.89–2.85]).</td>
</tr>
<tr>
<td>ACTG A5001/ ALLRT (Ribaudo et al., 2011)</td>
<td>Observational cohort of subjects randomized to ACTG clinical trials</td>
<td>5056</td>
<td>1704</td>
<td>36</td>
<td>1 year, and 6 years</td>
<td>0.7 (0.2–2.4)</td>
<td>1.9/1000</td>
<td>Lack of association over a 6-year period, over as-treated, and other sensitivity analyses.</td>
</tr>
<tr>
<td>Danish Cohort (Obel et al., 2010)</td>
<td>Retrospective cohort</td>
<td>2952</td>
<td>1761</td>
<td>67</td>
<td>Cumulative</td>
<td>2.00 (1.10–3.64)</td>
<td>2.4/1000</td>
<td>Risk of MI unchanged when time on ABC was introduced into the model, and remained elevated after cessation of ABC.</td>
</tr>
<tr>
<td>Veterans Administration (Bedimo et al., 2011)</td>
<td>Retrospective cohort</td>
<td>19,424</td>
<td>–</td>
<td>278</td>
<td>Cumulative</td>
<td>1.18 (0.92–1.50)</td>
<td>3.7/1000</td>
<td>No association of current ABC use and AMI (0.67; 0.43–1.03) or CVE (0.60; 0.45–0.79). HR for CVE: 1.16 (0.98–1.37). Current use of ABC associated with lower risk of CVE: 0.60 (0.45–0.79).</td>
</tr>
<tr>
<td>Veterans Administration (Choi et al., 2011)</td>
<td>Retrospective cohort</td>
<td>10,931</td>
<td>3235</td>
<td>501</td>
<td>Recent use (past 6 months)</td>
<td>1.48 (1.08–2.04)</td>
<td>6.0/1000</td>
<td>ABC use associated with CVE (2.10; 1.20–3.66), but not to coronary disease (1.43; 0.96–2.13).</td>
</tr>
<tr>
<td>Boston Hospitals (Trian et al., 2010)</td>
<td>Retrospective analysis</td>
<td>6517</td>
<td>1018</td>
<td>273</td>
<td>Any use</td>
<td>0.90 (0.70–1.10)</td>
<td>–</td>
<td>Cumulative or less recent ABC exposures not associated with CVE. Tenofovir use associated with heart failure, HR 1.82 (1.02–3.24), but not CVE (HR 0.78; 0.52–1.16).</td>
</tr>
<tr>
<td>Quebec (Durand et al., 2011)</td>
<td>Cohort and a nested case–control study</td>
<td>7053</td>
<td>–</td>
<td>125</td>
<td>Any exposure</td>
<td>1.79 (1.16–2.76)</td>
<td>3.9/1000</td>
<td>HR for current ABC exposure: 1.72 (1.10–2.71).</td>
</tr>
<tr>
<td>Magnificent Consortium (Rotger et al., 2013)</td>
<td>24 observational studies. Matched control study.</td>
<td>1875</td>
<td>–</td>
<td>571</td>
<td>Current</td>
<td>1.56 (1.17–2.07)</td>
<td>–</td>
<td>Lopinavir exposure associated with coronary artery disease (OR 1.36; 95% CI, 1.06–1.73).</td>
</tr>
<tr>
<td>NA ACCORD (Pellela et al., 2015)</td>
<td>Cohort, retrospective.</td>
<td>16,733</td>
<td>1948</td>
<td>301</td>
<td>Recent (prescription of ABC within the prior 6 months)</td>
<td>1.33 (0.96–1.88)</td>
<td>4.7/1000</td>
<td>In naive at ABC initiation: HR 1.95 (95%CI not given, p &lt; 0.05)</td>
</tr>
<tr>
<td>Swiss Cohort (Young et al., 2015)</td>
<td>Cohort, retrospective</td>
<td>11,856</td>
<td>4052</td>
<td>182</td>
<td>Cumulative</td>
<td>2.06 (1.43–2.98)</td>
<td>–</td>
<td>Current exposure decreases the risk to 0.27 (0.15–0.50), and cumulative exposure beyond 36 months not associated.</td>
</tr>
<tr>
<td>Veterans Administration (Desai et al., 2015)</td>
<td>Cohort, prospective</td>
<td>24,510</td>
<td>–</td>
<td>467</td>
<td>Current</td>
<td>1.50 (1.26–1.79)</td>
<td>2.8/1000</td>
<td>Increased AMI rates with current exposure to EFV (1.40; 1.19–1.66), 3TC (1.53; 1.34–1.75) and ZDV (1.41; 1.22–1.63). Antiretroviral combinations including these drugs or atazanavir also associated with AMI.</td>
</tr>
<tr>
<td>Kaiser Permanente (Marcus et al., 2016)</td>
<td>Cohort, retrospective</td>
<td>8154</td>
<td>704</td>
<td>75</td>
<td>Cumulative</td>
<td>2.2 (1.4–3.5)</td>
<td>3.8/1000</td>
<td>Increased CVD among ABC users when remaining on their initial regimen for ≥1 year (HR 2.7; 95% CI: 1.5 to 5.0); but a per protocol HR 2.1 (95% CI: 0.9 to 5.0, p = 0.11).</td>
</tr>
</tbody>
</table>


a Outcomes were time to first atherosclerotic cardiovascular event, defined as coronary, cerebrovascular, or peripheral arterial disease.
b Rates of coronary heart disease (defined by an acute presentation for MI or unstable angina, or by a coronary revascularization procedure (angioplasty or bypass surgery).c Data extrapolated from a graphic (fig 1) in the publication, numerical data not given (Trian et al., 2010).d Boldface highlights positive findings between abacavir exposure and AMI.
were naïve at inclusion in the cohort and the adjusted OR for short-term/recent abacavir exposure was 1.79 (95%CI, 0.74–4.27) (Lang et al., 2010). Nevertheless they conducted an elegant analysis excluding cocaine or intravenous drug users (a cause of non-atherosclerotic AMI), with 250 cases and 704 matched controls. The resulting OR for short-term/recent exposure to abacavir was 1.27 (95% CI, 0.64–2.49), therefore concluding no association between drug exposure and AMI. The inclusion of this single biasing factor impacted their result, therefore highlighting how important it is to identify and avoid potential effect-modifier variables in cohort analyses.

A recent elegant and provocative analysis from the Swiss Cohort suggests in a conventional Cox model, that recent — but not cumulative — exposure to abacavir increased the risk of a CVE (Young et al., 2015). However, using the new marginal structural Cox model that estimates the effect of abacavir as a flexible function of time, the risk of CVD was seen to increase paralleling the past exposure to abacavir, but only for a limited period, with exposure during the past 6–36 months causing the greatest increase in risk. Unexpectedly, current abacavir exposure had the opposite effect in this model: a protective effect (HR 0.36, 95% CI 0.23 to 0.55), and estimates of the effect of abacavir were not attenuated when an indicator for chronic kidney disease was added to the covariates used. A limitation of this study is that 45% of their 365 cardiovascular events were already included in the initial D:A:D cohort analysis. Actually, most of these subjects were included in the previous Magnificent Consortium, INSIGHT, and Swiss HIV Cohort analysis, that reported an association between current abacavir treatment and AMI (OR = 1.56; 95% CI, 1.17–2.07) (Rotger et al., 2013).

While again difficult to interpret, this study is great news for this debate, as most of these CVE should be captured in all 96-week randomized clinical trials (RCT) and would easily emerge in meta-analysis of RCT.

Therefore, probably it is not a matter of just seeing which cohort does find or not the association, or just increasing the number of subjects or events included in the analysis. It might be a matter of the methodology used to look at the problem.

1.2. How should non-cumulative drug-induced toxicity be assessed?

The proper way of assessing the association of short/middle-term or current severe adverse events and drug exposure are RCT (Table 2). They remain the mainstay for evaluating safety of investigational agents, being the only way of securing that populations compared are similar and the only existing difference between them is the exposure to the drug being studied (Chan-Tack et al., 2008). As the expected incidence of AMI is quite low (3-5 per 1000 patients/year in older studies, reduced in current studies to 2–4 per 1000 patients/year) no single RCT has power enough to reach a definite conclusion. Then the optimal research tool is a meta-analysis of RCT.

In a meta-analysis published in 2011, the risk of AMI or major CVE was not different between those receiving abacavir or tenofovir: RR 0.81 (95%CI:0.33,1.99) and 1.31 (0.76–2.26), respectively (Cruciani et al., 2011). The largest trial-level meta-analysis to date was done by the US Food and Drug Administration (FDA), and compiled 9868 subjects with 46 AMI events (incidence 4.7/1000 patients/year) and a mean follow-up of 1.43 person-years (Ding et al., 2012). They found no association between abacavir and AMI: risk difference = 0.008% with a (95% CI:-0.26%, 0.27%). They used the “risk difference” because the incidence of AMI was 0 in some trials. The corresponding Peto stratified OR was 1.02 (95%CI: 0.56, 1.83). However, this meta-analysis had some limitations as well. Despite having higher scientific accuracy, the number of AMI events captured through RCT was obviously lower than in larger cohorts, and therefore the power to reject the initial hypothesis raised in the D:A:D study was limited. The 95%CI values actually include the point estimation found in some cohorts (approx. 1.70) and therefore would not definitely exclude those previously reported results.

RCT meta-analyses not only minimize or eliminate confounding and selection bias but include only confirmed AMI events, which are always severe clinical adverse events fully monitored and reported in clinical trials. However, there is the possibility that subjects enrolled in these clinical trials might be at decreased risk of MI relative to the general HIV population due to being younger, not having comorbidities (hypertension, diabetes), and having less advanced HIV infection stages. Moreover, abacavir prescription was not randomized in some RCT, where the randomisation was focused on the third drug and the prescription of abacavir or tenofovir was an open physician choice.

Finally, the RCT meta-analyses did not analyse recent exposure but current exposure during a median follow-up of 1.43 PV and the “non-abacavir group” was again a mixture of different alternative drugs. Let’s remind that some patients allocated in cohort studies in the “non-abacavir” group could have been receiving some unusual regimens not included in standardized clinical trials.

1.3. The ultimate analysis?

Unfortunately, we must accept that there will be no feasible study to ascertain if the exposure to a given drug increases by merely 1.5–2.0 fold the rate of an adverse event that occurs in only 2–4/1000 persons/year. Furthermore, the previously reported excess risk of AMI among HIV-infected patients seems to be decreasing in some recent cohorts (Klein et al., 2015).

Meta-analysis of RCT offer high quality data, but cannot compile enough number of subjects and events, particularly if one wishes to ask the relevant clinical question: abacavir or tenofovir (not abacavir vs “non-abacavir”). Alternatively, cohorts may compile large numbers of individuals and AMI cases, but due to baseline channelsing and existing bias in many baseline characteristics and residual confounding, uncertainty remains in their results. In addition, the diagnosis of AMI or CVE and certain risk factors (eg, smoking) relies often only on administrative data (ICD-9 codes) in most cohorts.

1.4. The underpinnings of abacavir-induced AMI?

Most research groups have been struggling during more than 5 years to find an underlying mechanism or hypothesis that could justify the potential association to recent but not cumulative abacavir exposure to coronary (but not cerebrovascular) events. A review of this vast and often inconsistent literature is beyond the scope of this piece, but summaries are available (Bavinger et al., 2013; Costagliola et al., 2010; Martin-Iguacel et al., 2015). Investigations have focused on all known serum biomarkers (easy to undertake in serum samples but with low specificity) including markers of inflammation (such as high sensitive C-reactive protein, amyloid-P, amyloid-A, interleukin 6, interleukin 10, interleukin α, and macrophage migration inhibitory factor), markers of coagulation (D-dimer and fibrinogen), markers of platelet function (soluble P-selectin), and markers of endothelial function (vascular cell adhesion molecule 1 and intercellular adhesion molecule 1). No association with abacavir use has been found (Martin et al., 2010). Other investigations have also assessed carotid intima-media thickness or arterial stiffness, endothelial function, coronary endothelial cells in vitro, linkage to a metabolic syndrome, association with suppressed plasma HIV-1 viremia, in-vitro platelet
reactivity, leukocyte recruitment and accumulation, and many others (Martin-Iguacel et al., 2015). After all this huge research, no convincing mechanism has been found yet to explain a potential association with current (short term) but not cumulative exposure to abacavir. Obviously, the probability of finding by random a statistically significant association with some parameters in some studies parallels the number of studies done and the amount of variables included. Some of the most prominent findings have involved platelet aggregation. Carbovir triphosphate – the active metabolite of abacavir – has been associated to platelet hyper-reactivity in some ex vivo studies in a dose-dependent way through inhibition of soluble guanylyl cyclase or nitric oxide-mediated inhibition of platelet aggregation (Baum et al., 2011; Satchell et al., 2011; Emerson et al., 2016). However, findings have been inconsistent so far and would explain a steady increase paralleling cumulative exposure to the drug, an association not found either in cohorts or RCT.

The association of abacavir and endothelial dysfunction has been also conflicting. While current exposure of abacavir was independently associated with impaired endothelial function in some studies measuring flow-mediated vasodilation of the brachial artery (Hsieh et al., 2005), others did not find this association using high-resolution B-mode ultrasound in common carotid artery (Hsue et al., 2009), others did not so far and would explain a steady increase paralleling cumulative exposure to the drug in an escalating way, not found neither in cohorts nor RCT.

2. Conclusion

Some HIV-treating physicians prefer avoid abacavir and use tenofovir (or other alternatives, including tenofovir alafenamide [TAF] nowadays) in patients with medium-to-high CVR, and claim that “more research is needed”, always a wise and wary decision. Probably it’s not so easy. While this might represent an over-abundance of caution given the current state of knowledge, it could be unreasonable or even harmful. Most patients with enhanced CVR do have hypertension and/or diabetes and renal safety is of paramount importance in these subjects. So, administering a potentially nephrotoxic drug (certain with tenofovir fumarate, particularly when associated With boosted protease inhibitors in those subjects to avoid a potential increase in CVR (uncertain so far) would not necessarily be the safest clinical decision, and administering an NRTI-free regimen relies on a much lower evidence-based science and experience. TAF seems to reduce renal and bone toxicity to a neutral profile similar to abacavir, but long-term data (beyond 96 weeks) are still scarce (Sax et al., 2015). Therefore, these potential drawbacks of tenofovir might be removed from this equipoise and might radically change and reignite this debate.

So far, the overall available evidence is inconclusive and does not suggest an association between abacavir exposure and an increased risk of AMI and therefore has not been included in the package information by drug regulatory agencies (both EMA or FDA) in abacavir-containing products (Triumeq. Summary of prod, 2016; Triumeq. Highlights of pr, 2016).

“Association is not causality”. This is a gold standard rule in epidemiology. This association does not meet so far the Bradford Hill’s criteria for causation (mainly consistency, biological gradient, plausibility or coherence) (Hill, 1965).

Therefore, despite thoroughly investigating the drug, we do not currently have practice-changing evidence that abacavir causes a short/middle (but not cumulative) increase in the risk of AMI or CVE and have not found a clearly convincing pathophysiologic underlying mechanism.

As the French FHUDH colleagues concluded in their analysis (Lang et al., 2010), the association of AMI with abacavir cannot yet be considered causal. Medical decisions should be taken accordingly.

Conflicts of interest

Josep M Llibre has served as an advisor or speaker or has been awarded with grants for clinical research from Gilead Sciences, Merck Sharp & Dohme, ViIV Healthcare, Bristol-Myers Squibb, and Janssen-Cilag.

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