Overview of Studies Addressing Cardiovascular Disease Risk in HIV Infection and/or Treatment

Prepared for discussion at the Forum for Collaborative HIV Research workshop: HIV Infection, HIV Treatment and Risk for Cardiovascular Disease: an Independent Review of Ongoing Studies

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I. Introduction

The benefits of highly active antiretroviral therapy (HAART, also referred to as CART) – a combination of three or more drugs from one or more antiretroviral drug classes – is undisputed. Steep declines in morbidity and mortality have been documented in numerous studies [1-3], with a further reduction of AIDS and death in the late HAART era (post 1998) compared to the early HAART era (1996-1997) [4]. These achievements and the resulting opportunity for long term treatment have raised issues regarding long term drug toxicities to higher levels of concern.

Among the various HAART toxicities [5], those accumulating with time on treatment are of most concern especially as longer time on treatment coincides with aging of the population. These adverse events include lipodystrophy syndrome(s), dyslipidemia, insulin resistance and diabetes mellitus. The association of these factors with risk for cardiovascular disease (CVD), together with earlier reports of cardiovascular and/or cerebrovascular events in HIV patients [6-9], have prompted much discussion about the

risk for CVD in the treatment lifetime of a patient. While there is broad consensus that the benefits associated with prevention of HIV disease progression far outweigh toxicity related risk – at least for the exposure experiences thus far – concerns about long term treatment effects have contributed to the deliberations that have led to recommendations to delay initiation of treatment [5].

Any discussion of increased risk for CVD must be placed in the context of changes at the general population level with respect to CVD risk markers (obesity, diabetes, syndrome x), the demographics and HIV risk categories of the affected populations, and underlying chronic infection. Does HIV treatment simply magnify the risk for those with underlying risk, or does it induce risk for individuals who normally would not be considered to be at-risk?

In 1998 the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) requested studies to be initiated to answer questions regarding the prevalence and incidence of long-term cardiovascular complications and the relationship to body composition changes and metabolic abnormalities associated with CART. Data from two large studies [10,14,15] were presented to the CPMP, and they concluded that (quoted directly from [16]):

- The available results from the studies clearly demonstrate that the benefit/risk balance of antiretroviral treatment remains strongly positive.

- The long-term cardiovascular effect of combination antiretroviral therapy in HIV-infected patients has not been conclusively demonstrated and therefore concerns about the risk of cardiovascular disease should not lead to the withholding of CART when indicated for these patients.
- The ongoing studies of long-term cardiovascular complications (the DAD and the VA studies) should be continued for an extended follow-up time, at least until January 2005. The CPMP regards this extension and any additional follow-up that may be necessary to provide conclusive results as part of the ongoing commitment from MAHs *(marketing authorization holders).*

The two EMEA Oversight Committee funded studies looking at cardiovascular events in HIV infected patients are two of the largest ones initiated to date and the commitment to continued follow up will no doubt contribute to the increased understanding of the extent of risk. However, given the fact that these two studies have yielded contradictory conclusions (see below), and the fact that results from additional studies and meta-analyses have been presented, a review of all currently available data, including study design and methodology may be beneficial for interpretation and clarity in assessing risk.

Some of the questions faced today are:

- Is treatment of HIV infection associated with an increase in risk (excess risk compared to appropriate control populations) for CVD, and if so, what is the extent of this risk?

  - Who is more/less at risk?
  - Is risk attributable to protease inhibitors (PIs) only?
- What are the most productive investigative approaches?
  - Extension of current studies vs initiating new studies
  - What are the appropriate control populations?
  - What are the best study designs?
  - How reliable is data from cohort studies when the choice of initial regimen may be biased due to perceived risk?

This review is based on journal or conference publications identified by means of searching Medline and proceedings from major conferences in 2002 and 2003. Key points for all studies have been summarized in the Cardiovascular Risk in HIV Studies Summary Table. In addition to the publication reference, the summary table {ST} numbers will be included in the text below for easier navigation.

II. Studies that have looked at clinical manifestations of CVD

Twelve of the studies reviewed [10-15, 17-25, 31{ST 1-8, 10B, 11}] have analyzed clinical events related to cardiovascular and/or cerebrovascular disease, either in the form of hospitalization records or reported events. In some studies, endpoints were restricted to myocardial infarction; others included all cardiovascular disease events. Only two reports [17, 31{ST 3, 10B}] are based on data from randomized clinical trials; the remainder based on retrospective or prospective cohort data. Population sizes ranged from more than 36,000 [10 {ST 1}] to less than 50 [24 {ST 11}] patients.

Overall, investigators from 8 out of 12 studies concluded that there is evidence for increased rates of CVD in treated HIV patients [11-13, 15, 18-20, 23, 24 , 31{ST 1A, 1B, 2, 4, 5, 7, 8, 10 B}]. Three found no significant increase in CVD risk in HIV infection and/or treatment [10, 17, 25 {ST 1, 3, 11}]. One study found an increased risk associated with HIV infection, but not attributable to antiretroviral treatment [21, 22 {ST 6}].

Studies which concluded no increase in risk included a retrospective analysis of the VA database for CVD and cerebrovascular hospitalization events (n=36,766, 121,936 patient years) [10{ST 1}], a meta analysis of randomized clinical trials (n=10,986, 18606 PY) [17 {ST 3}], and a retrospective matched case control study (n=16 cases) [25 {ST 11}].

The first of these compared CVD specific hospitalization rates over time (1993-2001), with a total of 323,489 patient months of exposure to PIs (41.6% of the population, with a median exposure time of 17 months). All subjects were HIV-positive, and the population was primarily male. Thus the comparison was between HIV patient follow up during the HAART and the pre-HAART era. The second of the three studies compared MI events in patients randomized to receive PI vs. non-PI containing treatment, with a relatively short mean PI exposure (11.4-14.3 months), and with patients in the non-PI arm receiving what is now considered substandard treatment (2 nucleoside reverse transcriptase inhibitors NRTIs). Thus, although the comparison was between two treated populations, there would not have been equity in treatment efficacy with the potential for higher impact of chronic infection in the control group. The third study compared HIV patients with

ischemic CVD (n=16) to HIV patients without CVD, matched by age and sex. CVD was not related to PI use, although interestingly, there was a significant association with duration of NRTI and with lower CD4 cell count nadir.

The eight studies concluding that there is an increased risk encompass a total of 1, 07,573 patients. The studies varied in their ability to associate risk for CVD with specific antiretroviral treatment. The DAD study (n=23,468 with 36,199 patient years) [14, 15 {ST2}] found a low but significant independent association between combination antiretroviral therapy (CART) and MI (26% increase per year exposure compared to HIV positive patients not receiving treatment) without categorizing treatment. Their model included age, BMI, race, family history of CVD, smoking, sex, HIV risk category, originating cohort and pre-existing CVD; it did not include baseline levels of total cholesterol, triglycerides, diabetes, lipodystrophy and hypertension. An investigation of the database for Medi-Cal claims revealed that ART was associated with an increased risk of CHD in young (18-33 years) but not older individuals with HIV infection [13{ST1B}]. An analysis of the HERS database [24 {ST 8}] found a doubling in hospitalization rates for CVD in HIV infected women in the period 1994 – 2000, without providing information as to specific treatments.

The other studies [11, 12, 18-20, 23, 31{ST 4, 5, 10B}] have attempted to associate the risk specifically with protease inhibitor (PI) treatment. The French Hospital Database study (n=34,976 with 88,029 patient years) [11, 12 {ST 1A}] reported no significant difference in incidence of MI between the general population and patients treated with PI

for less than 18 months. However, the risk of MI among patients exposed to PI for 30 months or more was three times that of the general population [Standardized morbidity ratio (SMR)=2.9, 95% CI=1.5-5.0]. Iloeje et al [18 {ST 4}] looked at treated patients in the time period 1996-2000 and found that the risk for CVD and CHD events was doubled in patients using PIs, although absolute risk levels remained low. Interestingly, in their multivariate model, they did adjust for pre-existing hyperlipidemia, presumably the baseline value prior to initiation of PI treatment. The increased risk became more pronounced in a subanalysis that restricted patients in the PI category to those that had received a minimum of 60 days of PIs. The hazard ratios were also significantly higher in older patients. The HOPS study [19,20 {ST 5}] (n=5672) showed a very strong and significant association between CVD events and PI use in an univariate model; the association was still strong but not significant after adjusting for all other CVD risk factors (PI use, hypertension, smoking, diabetes mellitus, age, sex and evidence of dyslipidemia). Moore et al [23 {ST 7}] approached the question with a nested case control analysis in HIV infected patients undergoing treatment. They found increased risk to be associated with use of PIs as well as stavudine. Based on data from a randomized, controlled trial, Grover et al examined the effects of two PIs, nelfinavir and atazinavir, on blood lipid levels [31, {ST 10B}] and the impact of this on estimated CHD risk and life expectancy. In this case, the treatment comparison was one specific PI compared to another, as opposed to general PI treatment. The authors were able to discern a significance difference in estimated CHD risk in the two treatment populations.

The Kaiser Permanente study [21, 22 {ST 6}], based on confirmed hospitalization rates found an increase in risk for HIV positive men compared to HIV-negative controls. In contrast to the VA study, they found that HIV positive patients definitely have an increased rate for hospitalization due to CVD and/or CHD events. This would be in agreement with the HERS data [24 {8}]. However, whereas the HERS study did not include treatment information, the Kaiser Permanente study provided treatment information and reported no association with PI exposure. Nevertheless, hospitalization rates among HIV positive patients appeared to be lower prior to the introduction of PIs.

As is evident, the analytic approaches and methodology have varied considerably amongst these 11 studies. A standardized analysis plan may help to clarify some of the differences. This might include a standard set of baseline variables included in the models, and clearer definitions of exposure to specific drug classes.

III. Studies that have estimated/modeled risk based on risk factors

Four of the reviewed studies have estimated risk for CVD or CAD based on risk calculation algorithms [26-30{ST 9, 9A, 10, 10A}]. The French APROCO study [26 27{ST 9}] looked at HIV infected patients receiving PIs in comparison to the general (non HIV infected) population; El-Sadr and colleagues compared the CHD risk factors among HIV positive men and women enrolled in the SMART study [28, {ST 9A}]; Wall et al examined risk in HIV infected patients on or not on treatment as well as seronegative controls [29 {ST 10}], whereas Hadigan et al estimated risk in a cohort of HIV infected patients with lipodystrophy compared to matched non-HIV infected

controls from the Framingham study [30, {ST 10A}]. The APROCO investigators, using two different predictive models, found a significantly higher relative risk for HIV patients on PI compared to the general population; however the HIV patients also had significantly higher prevalence of CVD risk factors including some of the lipid profile components. El-Sadr and colleagues evaluated the 10 year CHD risk based on baseline characteristics upon study entry comparing men and women, rather than treatment groups or infected and non infected individuals. Wall and colleagues concluded that HIV infection and particularly PI use led to higher 10 year CVD risk estimates. In their multivariate model, only CD4 cell count remained independently associated; however, it is not clear what factors were included in the individual models. Hadigan's study [30 {ST 10A}] was interesting because it looked at a specific subpopulation of HIV patients – those with lipodystrophy. Because they included two control populations -- HIV infected patients without lipodystrophy and non-HIV infected individuals matched for sex, age, BMI -- they were able to distinguish between patients with and without lipodystrophy, showing that the 10 year risk for HIV patients with lipodystrophy was significantly higher than in matched HIV-negative controls, whereas the risk for HIV patients without lipodystrophy was not different from matched controls. Further adjustment for waist to hip ratio equalized the 10 year risk estimates for the lipodystrophy and control populations. Furthermore, they were able to distinguish between different patterns of lipodystrophy, with those suffering from lipoatrophy being more at risk.

Questions that are raised by these studies include

- What is the appropriate control group for risk estimation?
- Is the comparison between HIV patients on treatment to normalized population data a valid approach?
- What variables and risk factors need to be matched?

IV. Studies that have looked at surrogate markers

Six of the reviewed studies have used carotid intima media thickness (IMT) in relation to HIV infection and treatment. Presentation of the ACTG 5078 baseline data [32 {ST 12}] revealed no difference in IMT between HIV positive patients on PIs for more than 2 years, HIV positive patients not on PIs and HIV uninfected patients. Diabetes was an exclusion factor; PI patients did have significantly higher cholesterol and triglyceride values, as well as a significantly higher waist to hip ratio. Although these are cross sectional baseline results, the patients had been on PIs for at least two years prior to enrollment. In contrast, Hsue et al [33 {ST 13}}, looking at HIV infected patients only, reported that IMT increased at a significantly faster than expected rate over time, and this was associated with age and duration of PI use. There were differences between the two studies in the methodologies for assessing IMT with respect to location of measurement. One other study indicated a higher IMT value for PI using patients ([34 {ST 14}]. The remaining three IMT studies [35-37 {ST 15-17}], were either not designed to or not able to show an increase in IMT in association with treatment. Again, the importance of the right comparator group was highlighted: whereas the IMT was significantly greater between HIV patients prone to atherosclerosis and controls without this profile, it was not different when compared to controls with similar metabolic profiles [35 {ST15}]. Mercie

and colleagues controlled their model for all CVD risk factors, including total cholesterol, lipodystrophy and glucose disorders; thus, to the extent that these are treatment induced, it would be difficult to note an independent treatment effect [36 {ST 16}].

Three of the reviewed studies examined the association between HIV treatment and calcification scores [38-40 {ST 18-20}]. One study recruited only Black HIV positive men, and found significantly higher calcification scores in PI treated patients compared to the non PI group. They also had significantly higher cholesterol levels and mean corpuscular volumes [40 {ST 20}]. Acevedo and colleagues [40 {ST 18}] also found a higher calcification score in treated patients with severe dyslipidemia compared to HIV negative controls. In contrast, Wanke et al [39 {ST 19}] concluded that higher calcification scores were associated with non HIV and non treatment variables.

Two reviewed studies examined CRP levels. In the study by Henry et al, all patients were receiving indinavir, so the treatment association could not be investigated; nevertheless it was of interest that CRP levels were increased in virologically suppressed patients [41 {ST 21}]. In contrast, the study by Sklar et al concluded that neither reduction of viral replication nor reduced exposure to ART influenced CRP levels, although variability in CRP values was seen even among individuals with well-controlled HIV disease [42 {ST 21A}]. The authors concluded that this variability may be partly due to associations between CRP and traditional CV risk factors and CRP may be an important biomarker for determining CV risk in HIV patients.

Finally, two studies used endothelial dysfunction in relation to treatment with protease inhibitors [43, 44 {ST 22, 23}]. The first study examined the effect of 4 weeks of indinavir treatment on endothelial function in 6 HIV negative men [43, {ST 22}]. Looking at leg blood flow (LBF) in basal conditions and during intra-arterial infusion of vasoactive compounds they reported impairment of methacholine mediated increase in LBF during femoral artery infusion while the response to nitroprusside did not change. The study concluded that IDV monotherapy induces endothelial dysfunction in HIV seronegative men. The second study gave a similar result in a HIV positive sample [44, {ST 23}]. Using flow-mediated vasodilation (FMD) of the brachial artery (BA) to measure the endothelial dysfunction with and without the use of PI in 37 HIV positive adults, the investigators observed a significantly impaired FMD (2.6±4.6%). Patients not receiving PI (n=15) had normal FMD (8.1±6.7%). The study concluded that PI treatment in HIV patients induces atherogenic lipoprotein changes that lead to endothelial dysfunction.

V. Discussion

This overview of studies using different approaches to assessing cardiovascular disease risk associated with HIV treatment highlights several issues

- The scarcity of randomized trials

  All but two studies were based on cohort data. In an age when treatment choices are more abundant and decisions on when and with what to treat are made based on various factors, biases introduced into non-randomized studies may be difficult

to account for. On the other hand, the design and execution of randomized trials in this setting is a difficult task. Additionally, Phase II/III randomized clinical trials tend to have shorter durations of follow-up. This raises the question: are there other meta analyses that should be performed?

- Importance of standardized approaches

  This is illustrated by the various models that control for various combinations of baseline CVD risk factors. How can the treatment effect on these risk factors best be discerned from baseline and/or underlying risk levels?

- Need to define appropriate control groups

  What is the most appropriate control group in the current setting? How important is it to include HIV negative controls?

- Need to identify the most appropriate diagnostic techniques to address specific questions

The studies reviewed here include a wide array of demographics (all women, primarily non white; all men, all Black; all men, all White and various combinations in between). It will be necessary to sort out the differences in baseline and treatment induced risk in all these groups.

It is hoped that an open and collaborative interdisciplinary discussion between experts representing academia, industry, agencies and research networks and patient advocates will contribute to a greater level of clarity and consensus regarding the questions posed.

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