Pulmonary embolism and iatrogenic Cushing's syndrome after co-administration of injected-triamcinolone and ritonavir

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Understanding HIV epidemics: aggregate viral load metrics and ‘smoking guns’

Aggregate viral load metrics have numerous limitations that we have described previously [1,2]. We continue to urge caution around those limitations, but we will not repeat them here. Instead, as aggregate viral load metrics continue to be used and promoted, the recent contribution of Abu-Raddad et al. [3] to the ‘community viral load’ literature presents an opportunity to highlight some additional issues that we hope researchers and public health officials will consider carefully.

First, if use of these metrics is going to continue, we urge movement toward consistent, standardized definitions for specific aggregate viral load measures. The single phrase ‘community viral load’ has been used as a blanket term to describe aggregate viral load measures, calculated from a variety of samples, such as all HIV-positive patients in clinical care with available viral load data in a given setting [4], or all HIV-positive participants in a cohort study [5]. In this most recent example [3], yet another definition of ‘community viral load’ has been created: all antiretroviral therapy (ART)-naïve, HIV-positive people with available viral loads. This range of different definitions has led to confusion around the meaning of ‘community viral load,’ so we advocate a more standardized approach. The terminology developed by the Centers for Disease Control and Prevention for some types of aggregate viral load metrics [6] provides a starting place for defining common terms. In cases wherein a standardized term does not apply – such as for the metric studied by Abu-Raddad et al. [3] – we encourage explicit, descriptive designations other than ‘community viral load’ (for example, ‘mean pretreatment viral load’).

Second, we urge explicit statement of the assumptions behind every use of aggregate viral load measures. In each application of ‘community viral load’ to date, the aggregate viral load of the sampled population has been meant to represent the viral loads of some broader population, such as the entire HIV-infected population in a specific setting in a relatively recent time frame [4,5,7]. In the study of Abu-Raddad et al. [3], the viral loads were sampled among selected subsets of ART-naïve persons well after the epidemic started. Presumably, these viral loads were meant to represent the entire HIV-infected population in a given setting early in the epidemic – prior to the ART era – and (presumably) it was during this early period that the different ‘epidemic trajectories’ considered in this article [3] were assumed to have been established. Unfortunately, these assumptions were not clearly stated in the article. We suggest that such assumptions about target populations and times must be made explicit, and their validity carefully assessed. Furthermore, when comparisons are made across time or place, we encourage explicit discussion of the metric’s representativeness across these dimensions. For example, in this study [3], it would have been helpful to include statements that: the cross-setting comparison of viral loads available among ART-naïve individuals in each setting assumes that the measures (appropriately adjusted for CD4 category, pregnancy, and so on) are equally representative of early-epidemic ‘population viral load’ in the different settings; and that there may be some bias due to factors that were not controlled for, such as different distributions of acutely infected persons across the target populations, and the generally earlier conduct (in calendar time) of the included studies from North America compared to those from Africa [3].

Finally, as recently called for by Kretzschmar and Caraël [8], we urge careful consideration and discussion among HIV researchers about the criteria used to identify a ‘driving force’ of HIV epidemics. Such phrases have been used without sufficient clarity. For example, in this study [3], ‘community viral load’ was termed a ‘smoking gun’ for the explosive epidemic in sub-Saharan Africa, based on a relatively low population attributable fraction of 14% for the viral load effect. This conclusion was made despite the observation that models with and without the viral load effect in a representative African setting (Figure 2a in Abu-Raddad et al. [3]) both produced endemic HIV prevalence that was an order of magnitude greater than US HIV prevalence.

Our first two pleas – for standardized definitions of aggregate viral load measures and explicit statements about the assumptions surrounding them – are not specific to the study of Abu-Raddad et al. [3]. Our third plea – concerning definitions for terms like ‘driving force’ and ‘smoking gun’ – is confined neither to this particular study nor to the ‘community viral load’ debate overall. However, these types of concerns are becoming increasingly important as we continue to translate our improved understanding of factors influencing individual-level HIV transmission to their roles at the population level. Addressing these concerns is neither simple nor straightforward, but we believe such issues should be a high priority for discussion.

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References


Understanding HIV epidemics: aggregate viral load metrics and ‘smoking guns’

Powers et al. [1] provide valuable, thoughtful and thought provoking comments on our study [2]. In their first comment, they urge movement toward consistent, standardized definitions for specific aggregate viral load measures. We agree with this call. Furthermore, we believe this is timely with the increasing availability of HIV-1 plasma RNA viral load data for large subpopulations, and the growing role of viral load for clinical monitoring. We also acknowledge that our definition for community viral load in terms of all antiretroviral therapy (ART)-naive people with available viral load is different from the definition of the Centers for Disease Control and Prevention (CDC) that includes both untreated and treated HIV-infected people [3]. This operational definition, however, reflects our interest in examining the potential role of other factors such as coinfections in the HIV epidemic potential of populations in different regions around the world. Different viral load measures (including those articulated in the CDC guidance – population viral load, community viral load, in-care viral load, and monitored viral load) are useful to assess different questions and have different levels of feasibility [3]. For example, although population viral load is probably the optimal measure of ongoing epidemic potential, it is not possible to measure it in most settings because it includes undiagnosed HIV infection. At the other end of the continuum in the CDC guidance, monitored viral load is relatively easy to assess, and is informative with respect to quality of care, but may covey little about transmission potential at the population level.

We appreciate Powers et al. [1] suggestion of including explicitly specific assumptions in such analyses of viral load data. We implicitly assumed in our study that, biologically, HIV natural history, for ART-naive persons, has not changed throughout the epidemic. As noted in our study, we also agree that there could be factors, known or unknown, that could affect viral load measurements throughout the epidemic, and for which we were unable to control. Nevertheless, we did attempt to control for the differences in the distribution of HIV-infected persons across the different HIV stages by controlling for CD4 categories.

We also concur with Powers et al. [1] concern about the use of the term ‘driving force’. Causal attribution of factors within epidemics is an issue of intense discussion. We wish to clarify here that we used a stringent and conservative definition for attribution, based on the number of infections directly caused by heightened viral load, rather than those based on an estimate of the direct and indirect effects of heightened viral load. Including indirect effects, such as those due to onward transmission, would have even resulted in a considerably larger attributable role for heightened viral load.

Powers and colleagues, both here and elsewhere [4,5] have highlighted critical issues that must be dealt with to assess the role of viral load in HIV transmission. These issues are particularly timely given recent progress in HIV research, and the availability of a growing array of efficacious interventions to prevent HIV transmission by suppressing the viral load [5]. Our study reinforces the importance of these issues by suggesting that differences in viral load in ART-naive populations may have played a

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key role in shaping the different epidemic trajectories that we see across regions around the globe today.

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Pulmonary embolism and iatrogenic Cushing’s syndrome after co-administration of injected-triamcinolone and ritonavir

Ritonavir, commonly used in combination therapy for HIV-infected patients, is an irreversible inhibitor of the cytochrome P450 (CYP) enzyme CYP3A. As most corticosteroids are metabolized by CYP3A, a pharmacokinetic interaction is expected between ritonavir and corticosteroids, and patients may be at higher risk of iatrogenic Cushing syndrome (ICS). We report a case of a 51-year-old man known for C3 HIV, admitted for inpatient workup of a nonpruritic rash that persisted for 3 months. The rash appeared 1 week after two injections of triamcinolone acetone 40 mg in each elbow, administrated for bilateral epicondylitis. Topical clobetasol and triamcinolone acetonide 40 mg in each elbow, administrated for bilateral epicondylitis. Topical clobetasol and triamcinolone was 170-fold prolonged when co-administered with ritonavir.

Several steroid formulations associated with ICS were consecutively used in our patient [1–3], but triamcinolone injections done a few days before symptoms appeared are the most likely cause of ICS. Ramanathan et al. [4] estimated that elimination half-life of epidural triamcinolone was 170-fold prolonged when co-administered with ritonavir.

Cushing’s syndrome, either endogenous or secondary to steroids administration, increases the risk of developing a...
Table 1. Drugs with a predominant inhibitor effect on the CYP3A.

<table>
<thead>
<tr>
<th>Class</th>
<th>Inhibitor</th>
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<tbody>
<tr>
<td>Antibiotics</td>
<td>Erythromycin&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Ciprofloxacin</td>
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<tr>
<td>Clarithromycin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Isoniazide</td>
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<tr>
<td>Doxycycline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Roxithromycin</td>
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<tr>
<td>Antifungal agents</td>
<td>Miconazole&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Fluconazole&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Posaconazole</td>
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<td>Itraconazole&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Voriconazole&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Ketoconazole&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Anti HIV drugs</td>
<td>Lopinavir&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Atazanavir&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ritonavir&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Doravir&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Cardiovascular</td>
<td>Nifedipine</td>
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<tr>
<td>Amiodarone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Nitrédipine</td>
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<td>Dihydralazine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Verapamil&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Diltiazem&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Dronedarone&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Food</td>
<td>Liquorice&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Curcuma</td>
<td>Milk thistle (silibinine)&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Grapefruit&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Hormonal contraceptives</td>
<td>Gestodene</td>
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<td>Ethinylestadiol</td>
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<td>Psychotropics</td>
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<td>Fluoxetine</td>
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<td>Fluvoxamine</td>
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<tr>
<td>Nelfazodone&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Tyrosine kinase inhibitors</td>
<td>Nilotinib</td>
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<td>Dasatinib&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sorafenib</td>
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<td>Imatinib&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Others</td>
<td>Methylprednisolone&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Ciclosporine&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Cimetidine&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup>Potent inhibitors.
<sup>b</sup>Co-formulated with ritonavir.
<sup>c</sup>Highly active antiretroviral therapy boosters. CYP3A: cytochrome P450 enzyme 3A. Adapted from Samer et al. [10].

thromboembolic event, which occurs in 2.5 to 3.1 per 1000 persons-year [5–7]. The pathogenesis is not completely understood but depends on the degree of hypercortisolism and the duration of the disease. A possible underlying mechanism is cortisol-induced upregulation of transcription of various coagulation factors [8]. Apart from this, HIV has also been shown to be related with higher thrombotic risk ranging from 0.19 to 7.63% per year [9]. This is the first report of thrombosis associated with ICS secondary to ritonavir-steroid drug–drug interaction.

ICS is important to recognize and may be associated with thrombotic, metabolic, bone and infectious complications. Corticosteroids, even when given in nonoral formulation have the potential for clinically relevant drug-drug interactions with inhibitor of the CYP3A (Table 1) [10], especially in HIV-infected patients receiving ritonavir as part of their combination antiretroviral regimen.

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There are no conflicts of interest.

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References

Pope as prevention? Condom use by Catholics increased in five HIV endemic countries in sub-Saharan Africa during Pope Benedict XVI’s tenure

HIV continues to be a major global health challenge with 2.5 million new infections each year, 1.8 million of which take place in sub-Saharan Africa [1]. Condoms play a key role in limiting the HIV epidemic by acting as a physical barrier and keeping down the number of new strains [2]. In November 2010, in a historic shift, Pope Benedict XVI said that their use might be justified on a case-by-case basis to prevent the spread of HIV [3]. This appeared to be a relaxation of a hitherto uncompromising Vatican ban on the use of artificial contraception [4]. Whether Pope Benedict XVI’s policy shift affected condom use by the 170 million Catholics living in sub-Saharan Africa, and to what extent, remains largely unknown. Here, we briefly describe condom use by Catholics in five HIV endemic countries in sub-Saharan Africa during Pope Benedict XVI’s tenure, which lasted from April 2005 until February 2013.

We searched nationally representative household surveys conducted by the Demographic and Health Surveys (DHS) programme in sub-Saharan Africa, with survey waves completed at both ends of Pope Benedict XVI’s tenure. We then identified countries with available data on ‘condom use at last sex’ and religious affiliation, conditional on Catholics representing one of three major religious groups nationally. Figure 1 displays condom use for Cameroon, Mozambique, Rwanda, Uganda and Zimbabwe (HIV prevalence, 2.9–14.9%). Condom use by Catholics ranged between 2.3% and 23.8% in women and between 6.0% and 38.3% in men. Rates in Catholics were similar as in Protestants, whereas they were higher in Muslims in Rwanda and Uganda, and lower in Muslims in Cameroon, Mozambique, and members of the Apostolic Sect in Zimbabwe. During Pope Benedict XVI’s tenure, Catholics have increased condom use in Cameroon, Mozambique, Rwanda, Uganda and Zimbabwe, on average by 71.5% for men and women combined.

Sub-Saharan Africa is among the most religious areas in the world and boasts the fastest growing Catholic population [5]. It is possible that Catholics in Cameroon, Mozambique, Rwanda, Uganda and Zimbabwe somewhat increased their condom use as a direct result of Pope Benedict XVI’s policy shift or indirectly through the involvement of Catholic leaders, institutions and numerous organizations working locally. In addition, Pope Benedict XVI’s policy shift may have dissipated some of the stigma surrounding condom use among Catholics. Further research, however, should aim to examine potential effects among specific groups at risk for HIV, spill-over effects between religious groups and the potential effects of a papal policy that would fully legitimize condom use (rather than on a case-by-case basis). New evidence would prove instrumental as the incumbent pope shapes his policies.

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Fig. 1. (Continued)

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