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The ESR in HIV: A Neglected Parameter?

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Accepted wisdom in the assessment of a person with HIV is that the Erythrocyte Sedimentation Rate (ESR) is not a useful test. Although initially considered as an indicator of disease progression [1, 2], later studies disagreed [3] or demonstrated only a negligible fall in CD4 count with rising ESR [4].

Although the use of ESR to predict the development of AIDS is still under investigation in the developing world [5], it is considered less helpful in countries with easy access to CD4 monitoring. The ESR does not predict acute illness in HIV [6] and when measured, it is not uncommon to discover values in triple figures in otherwise asymptomatic individuals with normal CD4 counts: in one recent study, 27% of Tanzanian patients with an ESR > 120mm/hr still had a CD4 count greater than 200/mm³ [7]. As such, it is rare to find recent data on ESR levels in HIV positive people except from Africa [5, 7, 8], and it has not been published as an independent variable in any of the large prospective cohort studies.

I would argue that this approach is short-sighted, especially given what we have learned regarding cardiovascular disease in the last decade, across many disciplines. Indeed a chronically elevated ESR is potentially very informative:

- It reflects immune activation, correlating well with cytokines including Interleukin-6 and Tumour Necrosis Factor-alpha, a finding documented both in other chronic inflammatory conditions [9, 10] and in heart failure patients [11]. These molecules are known to be associated with endothelial damage, consistent with the presumed inflammatory nature of atherosclerosis [12]; predictably, both ESR and pro-inflammatory cytokines show a positive relationship with soluble endothelial markers including E-Selectin, von Willebrand Factor (vWF) and soluble Intercellular Adhesion Molecule-1 (sICAM-1) [10, 13, 14]. Inflammatory cytokines [14, 15] and endothelial markers [14, 16, 17, 18] have consistently been shown to be elevated in HIV positive patients, although their levels have not been stratified by ESR to my knowledge.
- It also reflects altered plasma viscosity, enhanced red cell aggregation and impaired microvascular blood flow. These phenomena, and their relationship to sedimentation rate, have been extensively studied in the context of HIV infection in the accessible retinal bed [19, 20, 21, 22] and are also suggested by in vitro evidence [23].

It is thus perhaps not surprising to find the following clinical evidence:

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- ESR independently predicts carotid atherosclerosis in both rheumatoid arthritis patients and healthy controls [24, 25].
- Current ESR [26] or 'cumulative ESR' [27] predict arterial stiffness in rheumatoid arthritis.
- ESR has consistently and repeatedly been shown to be an independent predictor of cardiovascular mortality both in patients with chronic inflammatory conditions [28, 29] and without [25, 30, 31, 32, 33, 34].

It would thus seem sensible to pay more attention to the ESR, especially now that cardiovascular disease potentially represents the greatest life-shortening threat to our patients. In terms of how to 'treat', the most obvious and attractive answer would be antiretroviral therapy, which reduces markers of immune activation [15], reduces serum markers of endothelial activation [18] and improves measurable endothelial function [35]. We await with interest the results of the Strategic Timing of Antiretroviral Treatment (START) study (clinicaltrials.gov reference NCT00867048), but I would postulate that the long-term advantage of early initiation of therapy would be greatest in the population with most immune activation and most impaired microvascular blood flow. It would seem logical from the evidence above that this is the group with significantly elevated ESR readings (it should be noted that not all HIV positive patients have elevated ESRs [3], and ethnic or environmental differences may contribute to this [36]: in fact chronic immune activation may be of greatest concern in Africa). If this is indeed the case then we would have a pre-existing, cheap and simple test to help guide these treatment decisions – rather than having to introduce high sensitivity CRP (hsCRP) or cytokine assays into routine laboratories.

There may be other treatment options: the Medical Research Council are currently investigating the use of the immunomodulatory drug hydroxychloroquine in antiretroviral-naïve patients (clinicaltrials.gov reference NCT01067417), and this may be of particular benefit in those with excessive immune activation and viscosity.

Other immunomodulators such as pentoxifyllene might also be considered. Another important drug class to consider would be statins. Despite the potential for drug interactions, their beneficial effect both on endothelial function and in reducing inflammation – including ESR – has been well documented [37, 38]. Improvements in endothelial function have been specifically demonstrated in HIV-positive patients taking pravastatin [39, 40]. Together with my belief that lipid targets should be lower in HIV positive people than the general population (more akin to high-risk groups such as diabetics, as has been suggested for those with chronic rheumatological conditions [41]) and the opportunity for 'learning compliance' with a daily tablet before the commencement of antiretrovirals, I would suggest that statins should be prescribed to antiviral-naïve patients far more commonly than they are in current practice.

Whichever strategy is adopted, the greatest risk appears to be leaving a high ESR 'untreated'. Many of our colleagues in rheumatology or haematology with greater experience of this parameter and its consequences would not even entertain such an idea.

In conclusion, I would urge those conducting large cohort studies to start measuring the ESR again: perhaps we will find that it *is* a useful test after all.

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