Remedicalizing an epidemic: from HIV treatment as prevention to HIV treatment is prevention

The response by Delva et al. [1] to our article contributes to a more integrated response to the challenges of the HIV epidemic to come. We agree that treatment and prevention should not be pitted against each other, even though this is often the case in the way in which funding is allocated and energies spent on the ground. In discussing the contribution of primary infection to HIV transmission, they are right to stress that local epidemics may vary significantly in this regard. The high proportion of acute infection to forward transmission has been documented in mainly MSM populations in the north, but there is comparatively little data on MSM or injection drug user populations in Africa, for instance, where circumstances differ. Our original commentary was written in response to a rather disturbing trend visible at the Vienna AIDS conference where activism and human rights were at times cast as impeding progress in the fight against AIDS. We agree that we must all work together and stress that involving communities affected by HIV and building their capacity to enact and sustain broader social transformations are necessary foundations for biomedical prevention to be effective over the long term. However, we caution that an overt emphasis on biomedical technologies risks eclipsing the importance of social change as the fundamental basis for prevention.

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Treatment-centred prevention: an integrated biomedical and social approach to HIV prevention

In their commentary ‘Remedicalizing an epidemic: from HIV treatment as prevention to HIV treatment is prevention’, Nguyen et al. [1] argue that the strong focus on ‘treatment-as-prevention’ (TASP) and other new technologies for HIV prevention signals remedicalization of HIV epidemics and a regression to the view of HIV as a medical problem best addressed by purely technical, biomedical solutions in the hands of biomedical professionals and scientists. They further question the potential of TASP to reduce HIV incidence and warn that remedicalization may come at the cost of reduced attention to the social, economic and sex inequalities which render people vulnerable to HIV infection and hinder access to HIV prevention and treatment.

We agree that recent operational research findings have reinforced the momentum for TASP [2–5]. However, we wish to offer a more nuanced view of the position of TASP in the HIV prevention arsenal, its potential impact on HIV incidence and the social costs and benefits associated with implementation of TASP.

We propose to replace the term and the narrowly biomedical connotation of TASP with a more holistic, inclusive notion of ‘treatment-centred prevention’ (TcP). TcP avoids ideology-based choices between old and new HIV prevention technologies, but implies combination prevention: HIV treatment as the cornerstone in synergistic programmes that offer a package of HIV prevention methods with proven effectiveness, tailored and sensitive to the local epidemiological and sociocultural contexts. HIV counselling and testing, presumptive treatment of sexually transmitted infections and medical male circumcision offer entry points for timely diagnosis and management of HIV infection. Similarly, early initiation of HIV treatment provides an opportunity for HIV-infected individuals and their partners to access biomedical and social support in their efforts to reduce the risks of HIV transmission.

As Nguyen et al. [1] correctly point out, ready access to antiretroviral therapy (ART) for eligible patients is in itself not sufficient for effective HIV prevention. Even if ART...
coverage was near universal, the time lag between HIV infection and initiation of ART would still be at least 5–10 years for most HIV-infected individuals under the CD4 cell count ART initiation thresholds currently used in resource-constrained countries. Assuming CD4 cell counts in HIV-infected people decline at an average of 60 cells/year [6], shifting the ART eligibility criteria from 200 to 350 or 500 cells/μl would decrease the period of unsuppressed viral load by 2.5–5 years on an average. Ongoing modelling work [7] suggests that such shifts have the potential to reduce the population HIV incidence by 40–50% over a period of 10 years, especially if interventions are prioritizing population groups at high risk of HIV acquisition and transmission, such as pregnant women and their partners. In contrast to the increases in risky sexual behaviour among MSM in San Francisco, cited by Nguyen et al. [1], evidence from Uganda and South Africa suggests that the expansion of ART has led to a decreased rather than increased sexual risk taking among individuals on ART [8,9]. The commentary also states that the impact of TASP is undermined by up to two thirds of HIV transmission events occurring during acute HIV infection which is most likely to take place before ART initiation. Although such high fractions of HIV transmission events during acute HIV infection may occur in certain individuals, this is generally not true: given the short duration of the acute stage of HIV infection [10], the acute infectivity spike is ‘wasted’ on the partner from whom HIV infection was acquired, unless the newly infected individual has concurrent partners. Although the prevalence of concurrency may be larger in Africa than in other parts of the world, it rarely exceeds 25% [11–14]. Dedicated analyses, integrating behavioural, clinical and epidemiological evidence, have estimated that even under the most liberal behavioural assumptions (a different partner for every sex act), no more than 31% of new infections are due to the acute stage of HIV infection [10,15].

In line with Nguyen et al. [1], we are of the opinion that – parallel to biomedical interventions – large-scale social and structural interventions to create sustained, equitable socioeconomic environments are long overdue [16–18]. We argue, however, that TcP has the potential to enhance rather than impede social transformation, community empowerment and health systems strengthening. Any TcP trial or programme large enough to impact on HIV incidence at the population level will affect a vast proportion of HIV-infected and HIV-uninfected people – either directly or indirectly. It is, therefore, of paramount importance to actively involve the relevant communities in the processes of design, implementation and monitoring of TcP programmes. Job creation and capacity building to accommodate the increased need for ample medical, psychological and social follow-up of individuals and couples should reinforce community ownership of TcP programmes. By extension, TcP may boost the sense of community empowerment to address deeply rooted social problems, including the societal burden of HIV. Moreover, if members of the community took a central role in the monitoring and evaluation of the impact of TcP on physical health, on psychosocial and economic well being and on health systems, their feedback would enable timely improvements to the programme. Lastly, horizontal integration and concurrent health systems strengthening is key in order to generate synergies between TcP and a host of ongoing health initiatives. Specifically, positive interactions should leverage efforts to reduce HIV-related stigma and discrimination, ‘normalize’ HIV testing and ART, prevent mother-to-child transmission of HIV, improve maternal health and the well being of children affected by AIDS and prevent interpartner violence. In conclusion, TcP may be a more social and effective approach to HIV prevention than portrayed by Nguyen et al. [1]. Unlocking the full potential of TcP, however, will require social and biomedical scientists to work with – not against – each other.

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References

Tenoforv and emtricitabine cerebrospinal fluid-to-plasma ratios correlate to the extent of blood-brainbarrier damage

Antiretroviral treatment is generally highly effective in controlling HIV replication in the central nervous system (CNS), although resistance associated mutations may be locally selected [1]. Drug passage into the CNS is known to be variable, being influenced by several parameters such as protein binding, molecular weight, lipophilicity, ionization, as well as by the presence of membrane transporters. According to a recently defined CNS drug penetration/effectiveness score, which was found to be associated to a significantly lower risk of viral replication in the cerebrospinal fluid (CSF), tenoforv and emtricitabine are classified as drugs with poor and good penetration, respectively [2]. However, a high individual variability of drug passage was recorded in pharmacoKinetic studies. In this setting, the possible role of disrupted blood-brain barrier (BBB) deserves consideration, as altered BBB has been frequently reported in neurological diseases [5], drug penetration into CSF is known to be significantly affected by disruption of BBB, but only limited evidence of this is available in case of HIV-infected patients receiving antiretroviral treatment [6].

We thus performed a pilot clinical study to investigate the effect of BBB disruption on tenoforv and emtricitabine passage into the CSF HIV-positive patients under treatment with Truvada-containing regimens who underwent a lumbar puncture for clinical reasons after having signed an informed consent were enrolled. Plasma and CSF tenoforv and emtricitabine concentrations were measured through a validated high-performance liquid chromatography-mass spectrometry system within a limit of detection of 2 and 1.5 ng/ml, respectively [7]. Albumin and immunoglobulin G (IgG) were measured both in plasma and CSF and albumin and IgG ratios were calculated; the Reiber index was used to evaluate BBB disruption. Data are expressed in median (interquartile range); association between variables were determined by Spearman test through SPSS, version 18.0 (SPSS Inc., Chicago, Illinois, USA).

Twenty-one patients were enrolled; 11 (52.4%) were men aged 38 (34–50) years old and presenting a BMI of 21.7 kg/m² (20–24.3). Drugs other than Truvada were mostly boosted protease inhibitors (66.7%) followed by non-nucleoside reverse transcriptase inhibitors (28.5%). Lumbar punctures were mainly performed to investigate neurocognitive disorders (29%) and MRI abnormalities (14%) and to follow up opportunistic diseases (29%); non-Hodgkin’s lymphomas, neurotoxoplasmosis and tubercular meningitis). BBB was altered in nine (42.8%) patients with albumin and IgG ratios, respectively, of 5.2 (4.7–8) and 5.4 (3.5–8).

Plasma and CSF were sampled at different time points but within 15 min from each other; median time after drug intake was 15 h (13.8–19.4). Tenoforv and emtricitabine plasma concentrations were respectively 49 (29.5–114) and 212 ng/ml (86.5–445.5). Tenoforv (TDF) CSF median concentration was 6 ng/ml (<2–8) and a linear correlation with plasma concentrations (P = 0.018) emerged. TDF CSF-to-plasma ratio was 0.05 (0–0.13).
Emtricitabine (FTC) CSF median concentration was 68 ng/ml (2.5–98), with a significant correlation to plasma concentrations (P = 0.02). FTC CSF-to-plasma ratio was 0.26 (0.05–0.41). A significant correlation between tenofovir and emtricitabine CSF-to-plasma ratios emerged (rho = 0.74, P = 0.002) (Fig. 1a). Both TDF and FTC ratios directly correlated to albumin ratios (respectively rho = 0.5 and P = 0.02, and rho = 0.05 and P = 0.05) (Fig. 1b and 1c); TDF ratios were correlated to IgG ratios (rho = 0.48, P = 0.03).

Some limitations of our study should be pointed out; a limited sample size, heterogeneous clinical conditions and a single sample per patient could potentially impact on our results. Nevertheless, being BBB abnormalities common during the course of HIV infection and pharmacokinetics parameters widely variable, these observations could improve our knowledge on CNS penetration of antiretroviral drugs.

In our patients, CSF-to-plasma ratios varied from 0–13% (for tenofovir) and from 5–41% (for emtricitabine), although median values were comparable to the ones reported in the literature [8,9]. The ratios of these two drugs with similar characteristics (high molecular weight and protein binding) were significantly correlated to each other, which suggest that the CSF penetration of both drugs can be influenced by common mechanisms and by alterations in the permeability of the BBB. Because both drugs seem to penetrate better in patients with altered BBB, we wonder whether barrier integrity should be considered as a factor potentially determining CNS concentrations. Barrier integrity might thus contribute to the high interindividual variability of drug penetration into the CNS. Our findings provide support to the recently established. Concordance of CSF viral load in 1221 volunteers in the CHARTER Cohort. 17th CROI (abstract), San Francisco, CA, USA 2010; 430.

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References


Bacterial translocation: a useful biomarker for immune activation and disease progression

Immune activation is by now well established as the main driver of the progression of HIV infection and its consequences [1–6]. Although HIV-specific killing of CD4 cells plays a major role in the pathogenesis of the acute phase of the infection, it is the continuous and persistent immune activation that characterizes the chronic phase of the infection and that is responsible for the profound CD4 cell attrition eventually resulting in AIDS. Likewise, the presence or absence of immune activation during simian immunodeficiency virus (SIV) infection is responsible for the presence of the AIDS-like disease in rhesus macaques or, for its absence, in the naturally occurring SIV infection in green monkeys and sooty mangabees, respectively [7,8]. HIV infection should, therefore, be perceived as a disease of chronic immune activation that is elicited by the specific immune response to HIV [6,9]. The dramatic clinical success of antiretroviral treatments (ARTs) that effectively suppress viral replication is primarily the outcome of the significant decrease in immune activation and the resultant immune reconstitution. Not surprisingly, therefore, disease progression is better correlated to immune activation, than to CD4 cell or viral load levels [10,11]. However, despite the very effective viral suppression achieved by ART, persistent immune activation is still present in a large proportion of patients and is probably responsible for the increased incidence of cardiovascular, metabolic and central nervous system (CNS) complications that develop in HIV-infected patients [12].

On this background, the introduction of the concept of bacterial translocation during HIV infection has been a very important development [13]. It has added a new player that accounts for immune activation that is not directly related to HIV but rather is the result of HIV infection. It has lent support to the central role the gastrointestinal tract and its associated lymphoid tissue play in the pathogenesis of HIV infection. And not less important, it has introduced new possibilities for treatment that may eventually affect the course of chronic HIV infection [14]. The hallmark of bacterial translocation during HIV infection is the damage to the intestinal mucosa that is caused in the early phases of HIV infection. This damage results in systemic dissemination of bacteria and bacterial products, which then cause and drive the immune activation of the host toward these elements. The presence of intestinal mucosal damage during HIV infection has been well documented in HIV-infected humans as well as in the SIV-infected primate models of HIV infection [15–17]. Studies of SIV-infected primates at various stages of the infection have revealed a clear and significant damage to the mucosa very early in the infection and have also demonstrated chronic changes that persist in the mucosa of the virus-infected animals. They have also demonstrated compellingly that such damage does not occur in the naturally infected primates that do not develop the AIDS-like disease [15]. Thus, the presence or absence of gastrointestinal damage seems to be an additional element distinguishing between animals that will or will not develop the AIDS-like disease.

At the present time, there are a number of biomarkers that can determine the presence and magnitude of bacterial translocation. The most useful and commonly used is circulating bacterial lipopolysaccharide (LPS) as determined by the limulus amebocyte lysate assay. However, increased serum levels of soluble CD14 (sCD14), EndoCab and circulating bacterial DNA are also in good correlation to bacterial translocation [17–19]. In this issue of the Journal, Marchetti et al. [20] report on the use of three of these biomarkers (i.e., circulating LPS, sCD14 and EndoCab) in predicting HIV disease progression. They demonstrate that circulating LPS is a very potent predictor of disease progression during the first years of the infection and independently of CD4 cell and HIV viral load. They suggest that circulating LPS should, therefore, be considered as a useful biomarker for HIV monitoring and evaluation in clinical trials. Although earlier studies have shown strong correlation of disease progression to other markers of immune activation, most notably cellular markers of activation—CD38 and HLA-DR on CD8, and Kit/6 [10,11,21], this study failed to show such correlation. This may be due to the poor condition of the thawed cells used in the study and the importance of doing such assays on fresh cells.

The importance of this report is in highlighting the potential impact of bacterial translocation on disease progression, in driving the immune activation and in the use of circulating LPS as a simple serum biomarker to...
monitor HIV disease. Such monitoring may become even more useful if new approaches for suppression of the chronic immune activation become available. As intensification of ART has not been effective in suppressing the persistent immune activation [22], new and more effective therapies should be developed for that purpose. As we enter the fourth decade of the AIDS epidemic, it is evident that one of the biggest challenges that AIDS medicine faces is to overcome this persistent chronic immune activation that probably accounts for the increased mortality and early development of cardiovascular, metabolic and CNS chronic diseases [12,23–26].

Though bacterial translocation has been demonstrated in both humans and primates infected with HIV and SIV, respectively, very little is known about the effects of other confections, and particularly infections involving the gastrointestinal tract, on this phenomenon. The neglected tropical diseases, and particularly helmint and schistosomal infections, are extremely common in most developing countries and affect very large populations [27]. As they reside and involve the gastrointestinal mucosa, they may cause varying degrees of mucosal damage and bacterial translocation, which can then induce chronic immune activation [28–30]. We have previously demonstrated that helmint-infected people have severe and chronic immune activation in the absence of HIV infection [9,31]. We have also suggested that such immune activation makes the host more susceptible to HIV infection and less able to cope with it [5]. Some recent studies on primates have lent support to our hypothesis, demonstrating that schistosoma-infected primates had higher simian HIV (SHIV) viral loads when infected with SHIV and were also much more susceptible to such infection in comparison with schistosoma-noninfected animals [32,33].

Taken together, these studies and that of Giorgi et al. [20] clearly demonstrate the importance of measuring bacterial translocation as a potent and useful biomarker for disease progression and continued immune activation. They also highlight the importance of the gastrointestinal tract in the pathogenesis of HIV infection and lend further support for the urgent need to study the histopathology and immunology of the gastrointestinal tract in diseases affecting the gastrointestinal tract, and particularly in the developing countries where neglected tropical diseases are so widespread and the AIDS epidemic is still spreading. Lastly, they also demonstrate the importance of developing new approaches for suppressing bacterial translocation [1] and hopefully decreasing the potential for the development of the long-term complications of the persistent immune activation in these patients.

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