We read with interest the novel strategy described by Papendorp and van den Berk [1] regarding instituting a standard highly active antiretroviral therapy (HAART) regimen (tenofovir, emtricitabine, and efavirenz) and raltegravir to reduce HIV-1 viral load rapidly in order to decrease perioperative infectious risk. Although raltegravir-containing HAART affords a more rapid viral load decline compared with other antiretroviral regimens [2], there remains a period of several weeks before virions are cleared from the plasma. This may represent an unacceptably long time to wait for urgent surgery. Building upon Papendorp and van den Berk's innovative concept [1] of using the pharmacodynamic properties unique to particular classes of antiretrovirals to reduce perioperative risk, we describe an alternative strategy that theoretically offers the same benefit within a much shorter time period.

Raltegravir, the first integrase inhibitor approved for clinical use, blocks incorporation of HIV-1 reverse transcripts into the host cell genome. Infected cells that have already undergone HIV-1 DNA integration at the time raltegravir is initiated will not be blocked from producing infectious virions. The rapid viral load decay seen in patients taking raltegravir may be the result of the blockade of a later stage of viral replication than other currently available antiretroviral drugs [3]. For example, it is likely that a larger population of infected cells can continue to produce virus in patients starting an efavirenz-based regimen than in patients starting a raltegravir-based regimen. With efavirenz initiation, all infected cells that have undergone reverse transcription will continue to produce virus, whereas, with raltegravir, only cells that have undergone viral integration will produce virus. This is likely the basis of the more rapid decay in plasma HIV-1 RNA levels in patients starting raltegravir [3]. However, with respect to occupational exposure, the critical issue is not the absolute level of plasma virus, but rather the level of infectious virus.

In theory, virions produced by previously infected cells in a patient starting an integrase inhibitor will be fully infectious if transferred to another host because integrase inhibitors act only on the integrase–viral DNA complex in newly-infected cells and not on the free enzyme in the virion [4]. The situation is different in patients starting protease inhibitors. These drugs inhibit the enzyme responsible for the cleavage of immature viral proteins within the virion during and after budding from the host cell. Previously infected cells, at all stages of replication, will continue to produce virions when a protease inhibitor is initiated [3]. For this reason, the viral load decay on protease inhibitor regimens is not as rapid as that observed with raltegravir. However, all virions produced in the presence of therapeutic concentrations of a protease inhibitor are immature and incapable of infecting a new target. Thus, within hours of initiating a protease inhibitor-based regimen, patients will have a falling viral load composed of immature, noninfectious virions that likely represent a minimal risk for blood-borne viral transmission.

In the case of protease inhibitors with a slow off rate, such as darunavir [5], enzyme inhibition may persist following occupational transmission of virus particles to a recipient for longer than the virion lifetime, affording complete protection. If the drug does dissociate, the virion would still need to complete the maturation process to become infectious. The nonnucleoside reverse transcriptase inhibitors potentially represent an intermediate case. In principle, they can bind to the reverse transcriptase molecules in virions, rendering them noninfectious. However, as soon as the inhibitor dissociates, reverse transcription could continue. Thus, in order to minimize the probability of occupational transmission, slowly dissociating protease inhibitors offer the most rapid way to reduce infectious virus in the plasma.

A potential concern of the drug regimen described by Papendorp and van den Berk [1] is the relatively low barrier to resistance of both efavirenz and raltegravir [6], which may present a risk to the patient long after surgery. This risk is compounded by initiating HAART on an urgent basis in a setting radically different from the outpatient HIV clinic, in which a support structure is ideally in place to maximize long-term positive patient outcomes. Protease inhibitor-based regimens have a significantly higher barrier to resistance than efavirenz or raltegravir and, for this reason, can often be given with confidence in settings where the presence of drug-resistance mutations cannot be fully assessed. In summary, both the mechanism of action and the superior resistance profile of protease inhibitor-based HAART argue for its use in this specific setting. In regard to blood-borne transmission risk, both the quality and quantity of virus should be considered.

Acknowledgement

Both authors contributed equally to the authorship of this correspondence.
Using HAART to decrease perioperative HIV-1 transmission risk

Thank you for your valuable comment in which you stated that by using protease inhibitors, the remaining virions will theoretically be noninfectious. The amount of infectious virions is crucial but difficult to determine in daily clinical practice. Lowering the absolute viral load and measuring this by routine assay offers a more graspable result. Therefore, we advocate the use of an integrase inhibitor to achieve a rapid decline in viral load. Combining this integrase inhibitor with a protease inhibitor instead of a nonnucleoside reverse transcriptase inhibitor offers the best of both worlds.

You mentioned that both efavirenz and raltegravir have a relatively low genetic barrier. We are not concerned about drug resistance in compliant treatment-naive patients using raltegravir for this purpose. Initiating antiretroviral therapy in a clinical setting offers the advantage of directly observed therapy with intensive counselling by specialized nurses. Also in the outpatient setting, very little drug resistance and virologic failure has been described in treatment of naive patients using raltegravir [1]. Furthermore, we do not favour the long-term use of raltegravir in a first-line regimen.

Reference


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Predicting the level of vaccine-induced cross-immunity necessary to eliminate HIV epidemics composed of multiple subtypes

In a very interesting study, Kiwanuka et al. [1] report significant differences in the rates of transmission associated with different HIV-1 subtypes in Rakai, Uganda. Controlling for other factors, they find the transmission rate of subtype A to be nearly double that of subtype D. The authors suggest that differential transmission rates among subtypes are important for HIV vaccine development and testing, understanding the dynamics of HIV-1 epidemics in different geographical regions and projections of the pandemic.

Over a decade ago, one of us (S.M.B.) constructed a mathematical model of an HIV epidemic composed of multiple co-circulating subtypes that differed on the basis...
of transmissibility [2]. This subtype model was constructed because preliminary data, collected in the mid 1990s, indicated that HIV subtypes might exhibit differences in transmission efficiency [3,4]. The model was used to predict temporal trends in prevalence of co-circulating subtypes and the potential impact of prophylactic vaccines. Specifically, the work investigated (theoretical) vaccines that would provide a degree of protection against infection by one subtype and induce cross-immunity against infection by another subtype. As the focus of the modeling work is so closely in line with the implications of [1], we now reexamine the subtype model using the remarkable data of Kiwanuka et al. [1] in order to gain insights into current epidemiological patterns and predict the long-term outcome of mass vaccination against HIV in Uganda.

Previously [2], the model was used to calculate basic reproductive numbers ($R_0$) for each of the cocirculating subtypes. $R_0$ represents the expected number of secondary infections caused by the introduction of one infectious individual into a completely susceptible population, and hence is a measure of fitness. The modeling showed that, in the absence of vaccination, the subtype with the largest $R_0$ would eventually outcompete and eliminate the other subtype. However, elimination would take over 100 years to occur and the prevalence of the less-fit subtype could remain high for several decades. If subtype D emerged before subtype A in Uganda, these results could explain why the less-fit subtype D is currently more prevalent than subtype A and is slowly decreasing (71–63% from 1994–2002), whereas the prevalence of subtype A is slowly increasing (15–20% from 1994 to 2002) [5].

As Kiwanuka et al. [1] point out, it is important to develop vaccines that are effective against several subtypes in order to control HIV epidemics. The previous modeling has shown that mass vaccination could result in several long-term outcomes: elimination of both subtypes, elimination of only one subtype, and persistence of both subtypes [2]. It was shown that which outcome would occur depends on the $R_0$, the vaccine coverage level, and three characteristics of the vaccine: take (i.e. the fraction of individuals for which the vaccine produces a protective immune response), degree of protection against one subtype, and the level of cross-immunity (i.e. degree of protection against the second subtype) [2].

The model was originally formulated to reflect transmission of HIV in a community of men who have sex with men. However, the model can be parameterized to reflect heterosexual transmission in Uganda because no significant differences between male-to-female and female-to-male transmission were observed by Kiwanuka et al. [1]. Doing so, we assume that the transmissibility of subtype A is approximately double that of subtype D [1] and that the average time to develop AIDS is 8 and 6.5 years, for subtypes A and D, respectively [6].

Figure 1 shows the long-term outcomes of mass vaccination given different levels of vaccine-induced cross-immunity, vaccine take and coverage. Calculations were made assuming the vaccine would provide an 80% degree of protection against infection by subtype A. It may be seen that, even using this highly effective vaccine, HIV elimination will only be possible if a high fraction of the population is effectively vaccinated (Fig. 1). For example, even if the vaccine take is 75%, it would be necessary to vaccinate over 90% of the population and for the vaccine to induce more than 30% cross-immunity against subtype D. If the level of cross-immunity is too low, elimination would not be possible and the less-fit subtype D could outcompete subtype A (Fig. 1). This occurs when the vaccine’s protection renders subtype A less fit than subtype D.

Our findings indicate that the presence of multiple subtypes will make HIV elimination more difficult and that mass vaccination campaigns may produce surprising results.

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Advantages of low-cost generic tenofovir instead of D4T for first-line antiretroviral therapy in Burma: a 2-year experience

Many third world AIDS treatment programs are contemplating an ‘upgrade’ to a less toxic long-term alternative to D4T. Few programs are aware that a Food and Drug Administration–certified generic equivalent of Atripla (Bristol-Myers Squibb & Gilead Sciences, LLC, Foster City, California, USA) is now available for US$ 15 per month. We have used this alternative for 2 years in Burma. It is cost-effective and has several advantages over the cheaper D4T regimen now used in resource-poor countries.

Burma (Myanmar), a poor country with 55 million people, has the worst untreated epidemic of HIV in Asia. It has poor health statistics, but, by best estimates, there are between 240 000 and 500 000 people living with HIV. The problem is worse along the borders with China, Thailand and India, and contributes greatly to cross-border epidemics in those countries.

The border region of Kachin state in northern Burma has the ingredients for the ‘perfect storm’ for an HIV epidemic. Here, heroin costs less than US$ 1 per fix, and there are large numbers of intravenous drug users. There are many gambling casinos with sex workers. Customers are Chinese and Burmese jade miners and teakwood workers, and the sex workers are local wives and mothers by day.

There is no Global Fund or PEPFAR support for HIV treatment in Burma and only 16 000 end-stage patients have been started on treatment, mostly by one non-government organization (NGO), MSF-Holland.

In August 2007, a grant from the Chicago-based Ann & Robert H. Lurie Foundation was used to start an HIV treatment program organized by the British NGO, Health Unlimited, along the border with China. The treatment effort took a new approach in this rural, high-prevalence area. Instead of relying on expensive laboratory equipment and frequent follow-up visits to detect signs of toxicity, we focused our limited resources on outreach rapid testing by mobile teams in rural villages. Those testing positive were referred to a central clinic for staging. Initially, without a CD4 machine, patients were staged clinically and stage 3 or 4 patients were started on treatment after two counseling sessions. Examinations, symptom reviews and adherence counseling (without laboratory monitoring) were done every 3 months thereafter. Now, a new CD4 machine allows treatment to be started at CD4 cell count of 350 cells/μl and monitored every 6 months.

An inexpensive generic form of tenofovir 300/ emtricitabine 200/efavirenz 600 was used as first-line therapy. This new combination has recently become available from Matrix, a totally owned subsidiary of the American generic company, Mylan, for 50 cents per tablet. Atripla (the branded equivalent) is produced by Bristol-Myers Squibb & Gilead Sciences, LLC, and is now the most common first-line AIDS treatment in the United States and Europe. But it costs US$ 55–65 a tablet. Even the discounted price (US$ 4–10 per tablet) offered to poor countries is too high for many programs in the developing world, when D4T costs a fraction of that.

However, the advantages of tenofovir over D4T are important: at 50 cents a day, it still costs twice as much as the D4T combination, but those costs can be offset by less need for laboratory monitoring. Without D4T, AZT, or nevirapine in the regimen, only symptoms and signs of side-effects need to be done. Hemoglobin, liver function and creatinine laboratory monitoring was not done (studies show tenofovir renal toxicity to be less than 1%). It is easier for patients to take one pill per day. Tenofovir has a more favorable resistance profile. Clinically, we have not seen any of the neuropathy or lipodystrophy that occur with D4T.

References

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HIV RNA levels in transmission sources only weakly predict plasma viral load in recipients

In a typical HIV-1-infected patient, plasma viral load (pVL) increases steeply in the first week after acute infection, then decreases as the immune system becomes activated, resulting in antibody seroconversion 3–13 days after infection and a full western blot pattern approximately 3 months later [1–3]. The so-called viral set point or steady-state viral load is reached after approximately 40–276 days from the acute infection moment [1]. Especially in the first few weeks of infection, differences are obvious in patients, especially with regard to time to peak load and time to viral load drop from peak to nadir [1], but also in the absolute viral RNA count. The viral set point is thought to represent a trade-off between viral replication capacity and repression of the virus by the host immune system. HIV-1 RNA levels vary considerably between individuals and also throughout the infection course in a particular individual. The viral load at set point is an important parameter, as it is strongly predictive of clinical progression [4,5]. Both the innate replicating capacity (fitness) of the virus strain and the strength of the host immune system would intuitively be the most obvious contributors, but it has been suggested that age, sex, shared human leukocyte antigen (HLA) alleles and duration of infection also contribute to the phenomenon [6]. The involvement of virus characteristics could easily be measured by analyzing the HIV replication capacity in donor–recipient pairs, wherein the viral load should be similar if viral replication fitness is the main determinant of pVL.

A cohort of transmission pairs, necessary to study comparative HIV-1 viral load dynamics, is not easy to establish. Viral relationships indicative of transmission should first be determined by phylogenetic analysis. Then, an acute phase plasma sample (to minimize the effect of immune pressure) of the recipient and a matching sample from the donor should be available. Hecht et al. [7] have analyzed early plasma samples from 24 such transmission pairs, all comprising men having sex with men (MSM), and reported a significant correlation between the HIV-1 RNA levels within the transmission pairs. However, they cautioned that these results should be reproduced in other cohorts to validate the finding. We here report a similar analysis in early samples from 56 sequence-verified HIV-1 transmission pairs, 60% MSM and 40% heterosexual, from The Netherlands. Recipients were sampled during primary infection, 20 recipients were in Fiebig stages III–IV (viral RNA+/−/western blot indeterminate) and 36 recipients were in Fiebig et al. [8] stages V (viral RNA+/western blot p31+) and VI (viral RNA+/western blot fully developed). HIV-1 blood pVL measurements were done using the Versant HIV-1 RNA 3.0 assay (Bayer Diagnostics Division, Tarrytown, New York, USA), NucliSens HIV-1 RNA (bioMérieux, Boxtel, The Netherlands) or m2000rt (Abbott Molecular Inc., Des Plaines, Illinois, USA). Viral loads of all couples were measured using the same assay. Samples from donors matched the time point when recipient samples were taken. Linear regression analysis was done with GraphPad Prism, version 5.01 (GraphPad Software, San Diego, California, USA) and correlation coefficients were calculated. In contrast to Hecht et al. [7], we do not find a strong correlation between plasma viral RNA levels within the pairs (Fig. 1). The Pearson coefficient of correlation (r) in our cohort was 0.25 for all 56 transmission pairs, 0.29 (range −0.17 to 0.65) for pairs when the recipients were in Fiebig et al. [8] stages III–IV and 0.06 (range −0.27 to 0.39) for pairs when the recipients were in Fiebig et al. [8] stages V–VI, suggesting that the correlation is completely lost when the infection progresses. The correlation coefficient (r) between viral RNA levels in donors and recipients was 0.55 in the 24 pairs studied by Hecht et al. [7], which were in similar early stages of HIV infection. A correlation coefficient (r) above 0.8 is usually denoted as strong and below 0.5 as weak, whereas r is equal to 1 represents a perfect correlation. So, in our transmission pairs, we detect only a
The low correlation between pVL in donors and recipients suggests that viral traits do contribute to pVL early in infection, but that other factors are equally or more important.

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Fig. 1. Relationship of HIV-1 RNA levels in 56 transmission pairs. Viral RNA levels in blood plasma from source individuals were correlated with viral RNA levels in recipients in the acute or early stages of infection. Correlations are shown for all 56 transmission pairs or for sources and recipients when the latter are separated according to the primary infection stage criteria of Fiebig et al. [8].