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Epidemiologically-Linked Transmission of HIV-1 Illustrates the Impact of Host Genetics on Virological Outcome

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Abstract

The diversity of HIV-1 and human genetics complicates our ability to determine the impact of treatment during primary HIV-1 infection (PHI) on disease outcome. Here we show in a small group infected with virtually identical HIV-1 strains and treated during PHI that only subjects expressing protective HLA alleles had lower viral loads following treatment discontinuation. These data suggests that genetic factors play a pivotal role in the outcome of HIV-1 infection despite early therapy.

Keywords

acute HIV-1 infection; HLA-B57; HLA-A11; Berlin patient; cluster

Introduction

Although subjects with primary HIV infection (PHI) present with distinct clinical syndromes, only a fraction of patients are diagnosed at this early stage of infection. However, it is during this initial phase that antiviral CD8⁺ T cell responses first emerge and high-level HIV-1 viremia is controlled by several logs to a set point(1,2). It has been proposed that therapeutic intervention initiated during PHI may alter the immune response of the host to HIV-1 and therefore allow for subsequent immune control of disease progression(3–6).

One of the strongest predictors of HIV-1 disease progression is host genetic factors(10,11), which may also play a key role in influencing control of viral replication following short-

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term treatment during the acute phase of the infection. For example, subjects expressing the MHC alleles HLA-B57, HLA-B27, HLA-B51 and HLA-A11, which dictate the specificity of the CD8+ T cell response, demonstrate an unusual ability to control viral replication regardless of early therapeutic interventions(10,12). In addition to host factors, viral genetics have been shown to play a substantial role in clinical outcome(13,14). Therefore, differences in both host and viral genetics can contribute substantially to disease progression in the setting of HIV-1 infections.

Unfortunately, however, it remains difficult to interpret the relative impact of an early therapeutic intervention during PHI in the presence of multi-faceted and heterogeneous factors such as host genetics and viral diversity. Here we report on a small epidemiologically-linked group, infected with virtually identical strains of HIV-1, in whom we had the rare opportunity to examine immune control and disease progression following treatment during PHI.

Materials and Methods

Study Subjects

All subjects were enrolled at the HIV-clinic Jessen, Germany [approved by the respective institutional review boards].

Viral Sequencing

Autologous gag and pol was sequenced from plasma RNA using population sequencing, as described previously(16). A neighbour-joining phylogenetic-tree was constructed using ClustalX [reference clade B consensus sequence (LANL)(accession no.xxxx-xxxx)]

Genetic Typing

All subjects were HLA typed using the SSP-Unitray system (Invitrogen). Screening for CCR5, CCR2 and SDF-1 polymorphisms were performed by PCR as described before(17).

Elispot Assays

HIV-1-specific CTL responses were quantified by IFN- γ -Elispot-assay using previously described optimal epitopes(18). A response was considered positive if >55 Spot Forming Cells (SFC)/10⁶ cells, and at least 3 > mean background activity.

Results

Identification of an epidemiologically-linked cluster of HIV-1 infected subjects

Three subjects with PHI (≤ 3 WB bands positive) were suspected of having been serially infected within 3 months from a chronically infected index subject following unprotected sex (Fig.1A). The status of the source person was unknown and has been tested HIV- five years ago. To verify the presumed linked transmission events, the gag and pol genes from each subject were amplified and sequenced from plasma RNA. Nearly identical HIV-1 clade B sequences were identified in each subject, with a mean pairwise nucleotide sequence identity between these sequences of 99.6%(± 0.2) (Fig.1B, SFig1). These data strongly support the transmission of highly related strains of HIV-1 between these epidemiologically linked subjects over a short period of time.

Subjects infected with nearly identical strains of HIV-1 exhibit different clinical courses

All patients immediately initiated HAART for a period of six months, achieving suppression of viral replication(Fig.1A). Within six months of cessation of therapy subjects "A", who

had already established chronic infection at the time of HAART initiation, and “C” exhibited viral load set points of 9×10^4 and 6×10^5 copies/ml, respectively, while subjects “B” and “D” exhibited lower viral load set points of 7×10^3 and 3.3×10^4 copies/ml, respectively (Fig. 1A). Thus, viral loads in subjects “A” and “C” ranged in the upper quartile, which is predictive of more rapid progression of disease, while subjects “B” and “D” ranged in the second and third quartiles, associated with slower progression of disease according to the MACS studies (19). These data indicate that subjects infected with an identical viral strain, and receiving HAART during the early phase of the infection, can have a substantially different viral setpoint after treatment discontinuation, suggesting that additional factors may be responsible for the distinct clinical courses.

Role of host genetics on control of HIV-1

To examine whether differences in host genetics might account for these differences in viral set points between subjects we examined multiple genetic loci previously identified to contribute to susceptibility to HIV-1 infection and rate of progression to AIDS (11). Here we assessed differences in HLA class I alleles (20), as well as polymorphisms within the chemokine receptors (21). While multiple promotor mutations in CCR5, CCR2, and SDF-1 were observed in this cluster of individuals. Only subject “B” was found to be homozygous for the potential protective A59029G-polymorphism in CCR5 (21) (Fig 1A). Notably, subjects “B” and “D” also expressed the HLA alleles HLA-B57 and HLA-A11 *respectively*, which are associated with control of HIV-1 replication and a more favorable disease progression (10). In addition, both subjects immunodominantly targeted specific CTL epitopes (HLA-B57-HW9(Nef), HLA-B57-TW10(Gag), HLA-A11-AK11(Gag)), which have been previously associated with control of viral replication (22,23) (**not shown**). The immunodominant response B51-TI8(Pol) in subject “C”, with a substantial higher viral load, was in contrast not present as an escape mutation had been transmitted within this epitope. In summary these data suggest that the expression of protective HLA alleles and the immunodominant targeting of key responses by these alleles, had a strong impact on the control of viral replication following cessation of therapy.

Discussion

The identification of tightly linked transmission cases of HIV-1 provides a unique opportunity to understand the different influences of host genetics and early antiretroviral therapy on disease progression. Here we present data documenting the rapid transmission of a strain of HIV-1 clade B within four individuals with different genetic backgrounds, which resulted in distinctly different virologic and immunological outcomes. The high degree of similarity of sequences derived from each subject suggested that little viral diversification had taken place within the first few weeks of infection, and therefore was not substantially contributing to differences in viral control.

After treatment discontinuation only subjects “B” and “D” maintained relative control of viral replication after cessation of HAART, in contrast to subjects “A” and “C”. Both subjects “B” and “D” expressed HLA alleles –especially HLA-B57- associated with control of HIV-1, and they mounted immune responses against immunodominantly targeted CD8 epitopes which have previously been associated with slower disease progression (22,23). This observation is emphasized by revisiting the “Berlin patient”, the first described case of spontaneous control of viral replication following short-term treatment interruption during primary HIV-1 infection (4). Several studies since then have investigated the role of early treatment during acute HIV-1 infection with or without interruptions but have provided contradictory results (6,7,9,24,25). A re-analysis of the host genetic factors of the “Berlin patient”, who to the present date exhibits control of viral replication, has recently revealed expression of the HLA-B57 haplotype (unpublished data). Therefore, it is likely that the

expression of HLA-B57 may have been one of the major contributor to the sustained control of HIV-1 replication in this subject, questioning the role of early interventional strategies for the sustained containment of HIV-1 following cessation of therapy. Taken together, these data suggests including host genetic factors into trials investigating the impact of treatment initiation during acute HIV-1 infection in order to accurately discern the relative contribution of early treatment on HIV-1 clinical outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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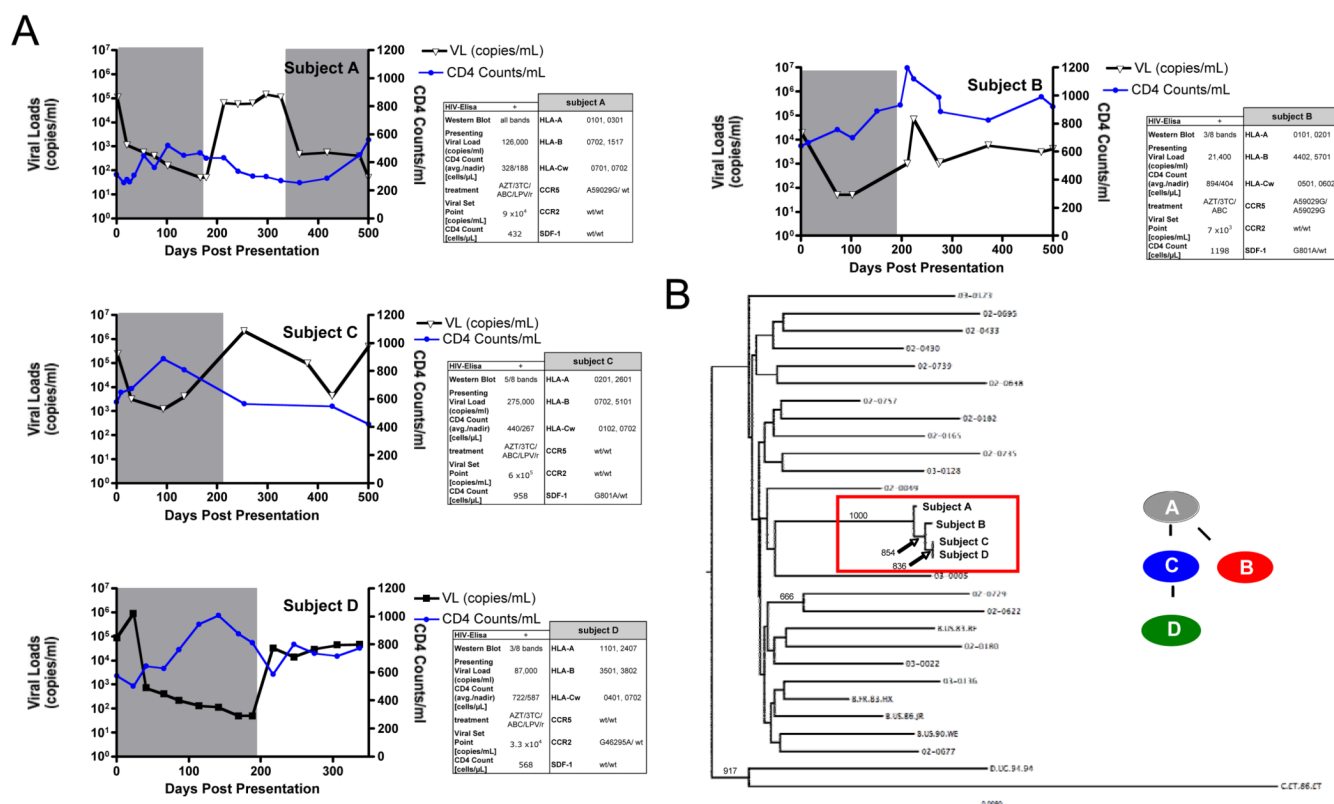


Figure 1. Epidemiologically-linked transmission of HIV-1

A) Longitudinal viral loads and CD4+ T cell counts are shown for all four subjects over a period of 900 days after presentation with primary HIV-1 infection. Lines in **blue** indicate the CD4+ T cell count, while lines in **black** indicate the viral loads in each subject. **Grey shaded** areas indicate the time on antiretroviral therapy in each subject. Inset shows the route of transmission of HIV-1 from subject "A" to subject "B" and "C", while subject "D" was subsequently infected by subject "C". **B)** HIV *pol* sequences from the four transmission subjects and nineteen other HIV chronic infected subjects from the same cohort were compared using a neighbour-joining phylogenetic tree. Sequences from the four subjects (**boxed**) cluster independently from sequences derived from other subjects. Scale bar indicates the genetic distance along the branches. Bootstrap values >600 are shown.