Temporal relationship between human Immunodeficiency virus type 1 RNA levels in serum and cellular infectious load in periheral blood

Blaak, H.; de Wolf, F.; van 't Wout, A.B.; Pakker, N.G.; Bakker, M.; Goudsmit, J.; Schuitemaker, H.

Published in: The Journal of Infectious Diseases

DOI: 10.1086/517327

Citation for published version (APA):
Temporal Relationship between Human Immunodeficiency Virus Type 1 RNA Levels in Serum and Cellular Infectious Load in Peripheral Blood

Hett Blaak, Frank de Wolf, Angélique B. van ’t Wout, Nadine G. Pakker, Margreet Bakker, Jaap Goudsmit, and Hanneke Schuitemaker

The age of disease in human immunodeficiency virus type 1 (HIV-1)–infected persons is associa ed with the level of virus in serum or plasma and the level of cell–associ a ed virus [1–4]. In ad dition, plasma levels of HIV-1 RNA early in infection are predictive of the rate of progression [5]. This latter finding, in which a h lage of CD4 T cell decline and disease progression, their emporal relationship is now fully understood. Therefore, we longitudinally compared virus RNA load in serum and infectious load in peripheral CD4 T cells from a heterogeneous group consisting of long–term survivors of HIV-1 infection and slow or rapid progressors of AIDS, either in absence or presence of syncy ium–inducing (SI)–HIV-1 varian s. In ad dition, he efec of rea men on virus RNA load in serum and on cellular infec ious load was analyzed for patients receiving an iviral therapy.

Subjects and Methods

Group A consisted of 23 par icipand s of the Amsterdam Cohort of patients on AIDS (ACS). Fifteen subjects were enrolled while still viral replication [6,7], favored plasma RNA load as a progression marker in HIV-1 infection and as a marker for initiation and evalua ion of an iviral therapy.

Cross-sectional analysis of 252 paired serum and peripheral blood mononuclear cell (PB C) samples derived from 54 human immunodeficiency virus type 1–infected persons revealed a correlation between HIV-1 RNA load in serum and infectious load in peripheral CD4 T cells after 18 months of follow–up and before an AIDS diagnosis (Pearson’s correlation coefficient \( r_p = 0.71 \), \( P < 0.001 \)) and during antiviral treatment (\( r_p = 0.78, P < 0.001 \)). To gain insight into the temporal relationship between both measures of virus load, longitudinally obtained samples from 23 persons with various clinical courses (slow or rapid disease progression, long–term survival) and 22 persons undergoing antiviral therapy (didanosine or didanosine, or both, or ritonavir) were analyzed. In general, the kinetics of changes in both measures of virus load were similar in the natural course of infection (78% of study participants) and during treatment (82% of participants). These findings suggest that PB C and serum represent closely related, if not the same, viral compartments.
navir were determined by use of reverse-transcriptase polymerase chain reaction (Amplicor HIV-1 monitor assay; Roche Molecular Systems, Branchburg, NJ). RNA levels in plasma and in serum were measured by NASBA correla e very well, with RNA levels in plasma being, on average, 0.5 log higher than those in serum [8]. For the participants receiving zidovudine and didanosine combination therapy, the number of proviral HIV-1 DNA copies in PBMC was determined using a competitive quantitative polymerase chain reaction [9].

The correla ion be ween serum RNA load and cellular infectious load was analyzed in 252 paired serum and cryopreserved PBMC samples derived from the subjects in groups A and B and from 9 additional persons, from whom only samples from a single time point were analyzed (n = 54). To avoid bias caused by repeated measurements for 1 person, the median of the paired measurements was analyzed by use of Pearson’s correla ion coefficient (r). In cases in which the number of samples was small, Spearman’s correla ion coefficient (r) was used. The woailed Fisher’s exact es and the Mann-Whitney U es were used to analyze the rela ionship be ween the frequency of productively infected CD4 T cells or serum RNA copies early in infec ion and the occurrence of an AIDS diagnosis.

Results

Cross-sectional analysis of RNA load and cellular infectious load. Virus load was analyzed in 252 paired serum and PBMC samples from 54 pa ien s. Analysis of the median of paired measurements of all par icpants revealed a significantly higher RNA levels in serum and the frequency of productively infected cells (n = 54, r = .52, P < .001) (figure 1A). Analysis of subgroups of samples, stra ified by rea men and s age of disease, indic ed ha bo h measures of virus load were highly correla ed in the period be ween the firs 18 mon hs of follow-up and AIDS diagnosis (n = 43, r = .71, P < .001) and during rea men (n = 26, r = .78, P < .001). However, nei her measure of virus load corre le ed in he firs 18 mon hs of follow-up (n = 18, r = .06, P = .8) or in the period af er an AIDS diagnosis (n = 8, r = -.05, P = .9).

S ra ifica ion of the samples by the absence or presence of SI varian s showed a similar correla ion be ween bo h measures of virus load in persons harboring bo h non-SI and SI varian s (n = 24, r = .53, P = .007) and in persons wi h only non-SI varian s (n = 42, r = .40, P = .008). Bo h measures of virus load were higher in persons wi h SI varian s (figure 1B). These da a confirm he exis ence of an associa ion be ween viral pheno ype and cellular infec ions [3] and also show a similar associa ion be ween viral pheno ype and RNA load in serum.

Virus load during the natural course of HIV-1 infection and during treatment. Three different profiles in serum RNA load and cellular infec ous load were observed in the 23 group A par icpants. Af er he firs 16 mon hs (range, 2–28) of follow-up un il AIDS diagnosis or he end of follow-up (mean ime,
Figure 2. Longitudinal analysis of HIV-1 RNA levels in sera and frequencies of productively infected CD4 T cells (TCID/10⁶ CD4 T cells) during natural course of infection (A) and during an antiviral regimen (B). A. For each pattern described in ex, 1 represents a rise is given: I, both measures of virus load remain stable at low levels (n = 5); II, both measures of virus load remain stable at moderate or high levels (n = 4); III, both measures of virus load increase (n = 9); and IV, RNA levels in sera remain stable and frequencies of productively infected cells increase (n = 5). ▼ = time of AIDS diagnosis; △ = time syncytium-inducing variants appeared. B. Represents persons reared with zidovudine (I; n = 10), didanosine (II; n = 6), ritonavir (III; n = 4), or zidovudine and didanosine in combination (IV; n = 2). In persons receiving both zidovudine and didanosine, proviral DNA load in CD4 T cells was also measured.

5.3 years; range, 2.0–9.4), (1) both measures remained stable (<1 log increase and/or <10⁴ RNA copies/mL of serum or <30 TCID/10⁶ CD4 T cells at the end of follow-up; n = 9); (2) both measures increased (>1 log; n = 9); or (3) the cellular infectious load increased while the RNA load remained stable (n = 5; figure 2A).

Mainenance of low levels of both measures of virus load was associated with long-term survival (5/5 were long-term survivors). Stable yet moderate or high levels (10⁴–10⁶ RNA copies/mL of serum and 50–70 TCID/10⁶ CD4 T cells) or an increase in both measures of virus load was associated with a progressive clinical course (12/13 were progressors). Of the 5 persons in whom RNA load remained stable a moderate or high levels while the cellular infectious load increased, 2 were long-term survivors and 3 progressed to AIDS within 2.8–5.5 years. In most patients (18/22) reared with antiviral–HIV-1 drugs (group B), changes in serum RNA load and cellular infectious load were similar. For both persons reared with the combination of zidovudine and didanosine, proviral DNA was additionally quantified but showed no change (figure 2B).

Predictive value of early virus load measures. In 22 patients from group A, cellular infectious load was measured a
Discusión

En este estudio, la correlación entre los niveles de RNA en la sangre y la carga infecciosa celulares en el interior de los leucocitos fue significativa en el grupo 1 (n = 12) con un valor de correlación de 0.62 y una p-value de 0.001. En el grupo 2 (n = 10) con un valor de correlación de 0.37 y una p-value de 0.12. La correlación entre los niveles de RNA en la sangre y la carga infecciosa celular en PBMC fue significativa en el grupo 1 con un valor de correlación de 0.75 y una p-value de 0.001, mientras que en el grupo 2 con un valor de correlación de 0.45 y una p-value de 0.18.

Se observó una disminución de células del tipo CD4 en la sangre en el grupo 1 con un valor de correlación de 0.62 y una p-value de 0.01, mientras que en el grupo 2 con un valor de correlación de 0.37 y una p-value de 0.12. Se observó una disminución de células del tipo CD8 en la sangre en el grupo 1 con un valor de correlación de 0.58 y una p-value de 0.02, mientras que en el grupo 2 con un valor de correlación de 0.39 y una p-value de 0.15.

En general, se observó una correlación significativa entre los niveles de RNA en la sangre y la carga infecciosa celular en PBMC en el grupo 1, pero no en el grupo 2. Sin embargo, se observó una correlación significativa entre los niveles de RNA en la sangre y la carga infecciosa celular en PBMC en el grupo 2, pero no en el grupo 1.
infected load remained stable at moderate high levels. Conversely, we found that some persons who maintained stable and high CD4 T cell counts over prolonged periods had either increasing cellular infected load and stable, moderately high infection: progression of disease is associated with a shift from memory- T-cell– tropic virus populations. J Virol 1992;66:1354–60.


Acknowledgments

We thank Silvia Broersen, Margreet Brouwer, Agnes Holwerda, Jeane van der Huls, Susana Kerkhof-Garde, Neelke van der Huls, Susana Kerkhof-Garde, Neelke Kooistra, Ana-Maria de Roda Husman, Dawn Clarke, and Frank Miedema for critically reading the manuscript. We are greatly indebted to Silvia Bruinen for providing proviral DNA data; Charles Boucher and Menno de Jong for providing Roche RNA data; and Michel Klein, Maar van Kooistra, Ana-Maria de Roda Husman, Dawn Clarke, and Frank Miedema for critically reading the manuscript. We are grateful to the Academic Medical Center AIDS clinic for their participation.

References


