Glut1 expression on CD8^{dim} T cells is associated with immune recovery in HIV-1-infected individuals

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To the Editor: Immune non-responders (INRs), who account for approximately 10–40% of human immunodeficiency virus (HIV)-infected individuals, have received effective treatment and exhibit persistent suppression of viral replication, but their CD4$^+$ T-cell counts are not restored. They are likely to have an increased risk of non-acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality compared with immune responders (IRs).[1] CD8$^+$ T cells play an important role in viral infection, and the functional properties of circulating CD8$^+$ T cells have been associated with immune control of HIV. High CD8$^+$ T-cell counts are beneficial for persistent viral decay and CD4 T-cell recovery in immune-restored patients during long-term antiretroviral therapy (ART).[2] Two subsets of CD8$^+$ T cells have been identified according to their intensity of CD8 expression: CD8^{bri} and CD8^{dim} T lymphocytes. It was demonstrated that CD3$^+$CD8^{dim} T cells, with weaker function than CD3$^+$CD8^{bri} T cells, were associated with disease progression during HIV infection.[3] However, dynamic changes in the numbers of CD8^{bri} and CD8^{dim} T cells in INRs and IRs before and after ART have not yet been reported.

As a hallmark of HIV infection, metabolic dysfunction of immune cells also has impact on pathogenesis and disease progression. Low CD4$^+$ T-cell count is associated with hyperactive glucose metabolism.[4] Glucose transporter 1 (Glut1) is the primary glucose transporter on T cells, and activated cells meet their increased metabolic requirements by increasing Glut1 expression, which leads to enhanced T-cell effector function.[5] Thus, identifying differences of Glut1 expression in cell surface and the different fates of cells is of great interest. It was shown that HIV infection led to increased expression of Glut1 on CD8$^+$ T cells.[6] However, there was a relative scarcity of research focusing on the role of Glut1 on CD8$^+$ T cells and their subsets during HIV infection, especially in INRs.

We performed this study in Beijing Youan Hospital, Capital Medical University, China. A cohort of 20 healthy controls and 40 HIV-1-positive individuals (20 INRs with poor CD4$^+$ T-cell recovery [<500 cells/μL after four years of ART] and 20 IRs with immunological restoration [>500 cells/μL after four years of ART]) were enrolled. Detailed information on the donors is listed in Supplementary Table 1, http://links.lww.com/CM9/B812. All relevant experiments in this study were approved by the Beijing Youan Hospital Research Ethics Committee (Nos. 2020-063; 2021-161), and written informed consent was obtained from each participant following the *Declaration of Helsinki*. Detailed experimental procedures and statistical methods are shown in Supplementary Materials, http://links.lww.com/CM9/B812. A P value <0.05 was considered to indicate a statistically significant difference.

As shown in Supplementary Table 1, http://links.lww.com/CM9/B812, no significant differences in number or age were present between the groups. The CD4$^+$ T-cell count of the IRs was higher than that of the INRs ($P = 0.018$ before ART; $P < 0.0001$ after ART). The CD8$^+$ T-cell count of the INRs was similar to that of the IRs before ART, but the CD8$^+$ T-cell counts in the IR group were higher than those in the INR group ($P < 0.0001$) at the time of analysis after ART. No difference was observed in the ratio of CD4/CD8 T cells between the two groups before and after ART.

As was shown in the study, the absolute CD8$^+$ T-cell count in INRs and IRs showed no difference before ART. After 4-year ART, an increasing trend was shown in CD8$^+$ T-cell count of IRs compared with the case before but without statistical difference. The CD8$^+$ T-cell count of IRs after ART was significantly higher than that of INRs [Figure 1A]. The proportion of CD8^{bri} T cells in INRs before ART was higher than that in healthy

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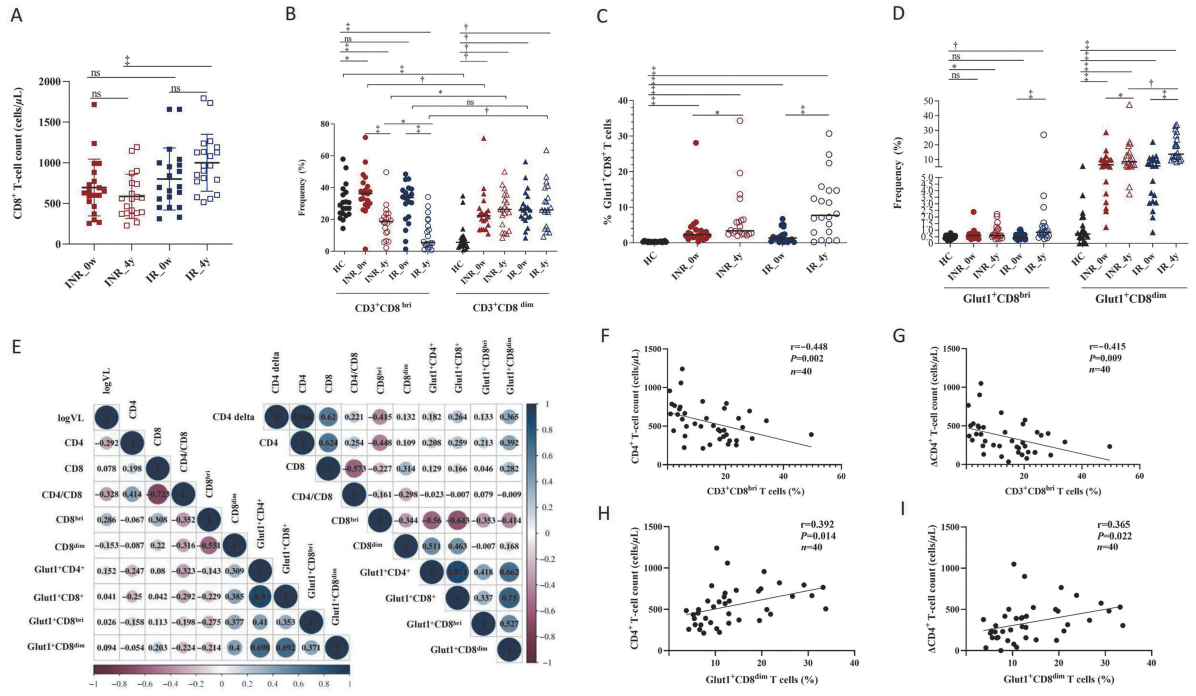

Figure 1: Glut1 expression on CD8^{dim} T cells is associated with immune recovery in HIV-1-infected individuals. (A) Absolute CD8$^+$ T cells in INRs and IRs before and after ART. (B) The frequencies of CD3$^+$ CD8^{bri} and CD3$^+$ CD8^{dim} T cells in INRs and IRs before and after ART. (C,D) The expression of Glut1 on CD8$^+$ T cells and the two subpopulations in INRs and IRs before and after ART. (E) Dot heatmap showing Spearman rank correlations between selected cell subsets and clinical indicators in HIV-1-infected patients (both INRs and IRs) before (left) and after 4 years of ART (right). (F,G) Correlations of the frequencies of CD3$^+$CD8^{bri} cells with CD4$^+$ T-cell count and ΔCD4$^+$ T-cell count. (H,I) Association of the percentage of Glut1$^+$CD8^{dim} cells with CD4$^+$ T-cell count and ΔCD4$^+$ T-cell count. Each dot represents one participant. Associations were evaluated using Spearman rank correlation test. $^*P<0.05$, $^\dagger P<0.01$, $^\ddagger P<0.001$. ART: Antiretroviral therapy; Glut1: Glucose transporter 1; INR: Immune non-responders; IR: Immune responders.

subjects ($P<0.05$), but the difference in the CD8^{bri} T-cell proportion in IRs was not statistically significant compared to HC [Figure 1B]. In addition, after 4 years of ART, the frequency of CD8^{bri} T cells in both INRs and IRs obviously decreased, but the percentage of CD8^{bri} T cells in INRs was still higher than that in IRs, and the difference was statistically significant. Moreover, the frequency of CD8^{bri} T cells was obviously increased in HIV-1-infected patients compared with healthy controls, but there was no statistical significance in the frequency of CD8^{dim} T cells in INRs and IRs before and after ART. In addition, before ART, the percentage of CD8^{bri} T cells was higher than that of CD8^{dim} T cells in INRs, but after ART, the frequencies of CD8^{bri} T cells were lower than those of CD8^{dim} T cells in INRs; this result tended to be statistically significant. The frequencies of CD8^{bri} T cells in IRs before ART were similar to those of CD8^{dim} T cells, while those in IRs after ART were significantly lower than those of CD8^{dim} T cells [Figure 1B]. To further explore the level of glucose metabolism in CD8$^+$ T cells in HIV-infected adults, the expression level of Glut1 on CD8$^+$ T cells was evaluated in this study. As shown in Figure 1C, Glut1$^+$CD8$^+$ T cells were expanded in HIV-1-infected patients, and the expression of Glut1 on CD8$^+$ T cells was further increased after 4 years of ART. Additionally, before ART, the percentage of Glut1$^+$CD8^{bri} T cells did not differ between HIV-infected individuals and healthy controls; however, after 4 years of ART, the number of Glut1$^+$CD8^{bri} T cells in IRs significantly increased compared with that at the beginning of ART, but INRs did not exhibit the same change [Figure 1D]. In addition, HIV-1 infection led to the expansion of Glut1$^+$CD8^{dim} T cells in both INRs and IRs. Moreover, after 4 years of ART, the frequencies of Glut1$^+$CD8^{dim} T cells in INRs and IRs were significantly higher than those before ART. Furthermore, the frequency of Glut1$^+$CD8^{dim} T cells in IRs was significantly higher than that in INRs after ART [Figure 1D].

To explore the possible role of Glut1 in the recovery of immune function in HIV-1-infected patients (both INRs and IRs), the associations of Glut1 expression on CD8$^+$ T-cell subpopulations and HIV-1 clinical parameters, including CD4$^+$ T-cell count, CD4/CD8 ratio, delta (Δ) CD4$^+$ T-cell count, and HIV-1 viral load, were analyzed. Statistical correlations were analyzed using matched measurements presented in a dot heatmap. The left half shows the correlations at the time when ART was initiated, and the right half shows the correlations 4 years after ART [Figure 1E]. The frequencies of CD8^{bri} T cells showed significant negative correlations with CD4$^+$ T-cell count and ΔCD4$^+$ T-cell count in HIV-infected individuals after 4 years of ART (Figures 1F and 1G, $r=-0.448$, $P=0.002$; $r=-0.415$, $P=0.009$, respectively). In addition, Glut1$^+$CD8^{dim} T cells were weakly positively correlated with CD4$^+$ T-cell count and ΔCD4$^+$ T-cell count ($r=0.392$, $P=0.014$; $r=0.365$, $P=0.022$) in HIV-1-infected patients who received 4 years of ART [Figure 1H, I]. These data show that insufficient Glut1$^+$CD8^{dim} T cells may be associated with poor immune reconstitution in HIV-1-infected patients.

In this study, a dramatic increase in the frequencies of $CD8^{bri}$ and $CD8^{dim}$ T cells was observed during the chronic stage of HIV-1 infection. ART has a limited effect on the frequency of $CD8^{dim}$ T cells since no significant change in the proportion of $CD8^{dim}$ T cells could be seen in either INRs or IRs before and after ART. However, ART can markedly reduce the proportion of $CD8^{bri}$ T cells, especially in IRs. Considering that the frequencies of $CD8^{bri}$ T cells were negatively correlated with $CD4^+$ T-cell count and $\Delta CD4^+$ T-cell count, we hypothesized that the large number of $CD8^{bri}$ T cells may be detrimental to immune reconstruction in INRs.

Palmer *et al*[4] have found that the number of $CD4^+$ T cells that express Glut1 is increased in HIV-1-infected, treatment-naïve persons. This number is decreased by suppressive ART but not completely normalized when compared with uninfected individuals. High circulating levels of these cells are associated with immune activation and a low $CD4^+$ T-cell count in patients, regardless of treatment status. However, our results have shown that $CD8^+$ T cells, especially $CD8^{dim}$ T cells, had increased Glut1 expression after HIV-1 infection, which suggests that chronic HIV-1 infection may result in abnormal glucose metabolism in $CD8^+$ T cells. In addition, after 4 years of ART, Glut1 expression on $CD8^+$ T cells further increased, and this phenomenon was more obvious in IRs. Given that increasing glycolysis leads to enhanced T-cell effector function and that $CD8^+$ T cells exhibit weaker function in INRs than in IRs,[7] we speculated that the deficiency of $CD8^+$ T-cell function in INRs might be related to the lack of Glut1 expression. Therefore, regulating Glut1 expression on $CD8^+$ T cells might be a potential option for immunotherapy in INRs.

In conclusion, our study revealed the dynamics of $CD8^{bri}$ and $CD8^{dim}$ T cells and the expression of Glut1 on these two subsets in INRs and IRs before and after ART, and our results suggest that higher frequencies of $Glut1^+CD8^{dim}$ T cells have the potential to predict better recovery of $CD4^+$ T cells after ART, possibly indicating a novel target for HIV immunotherapy.

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Conflicts of Interest

None.

Data sharing

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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