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The monoclonal CD4 antibody M-T413 inhibits cellular infection with human immunodeficiency virus after viral attachment to the cell membrane: An approach to postexposure prophylaxis

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ABSTRACT **Infectious cellular uptake of human immunodeficiency virus (HIV) is initiated by a complex sequence of interactions between the viral envelope gp120/gp41 complex and the cellular CD4 receptor resulting in the exposure of a hydrophobic region of gp41 that mediates the irreversible fusion of the virus with the cell membrane. Here we show that viral penetration into a susceptible cell can be inhibited by the high-affinity monoclonal CD4 antibody (CD4 mAb) M-T413 even when it is added as late as 30–120 min after the initial contact of virus with the cell membrane. Inhibition of infection was assessed by monitoring cultures for 34 days after exposure to virus using four different methods simultaneously, including detection of viral DNA by PCR. The interval during which HIV remains sensitive to postbinding neutralization by CD4 mAb depends on strain of virus and type of target cell. Preparations of recombinant soluble CD4 (and the immunoadhesin CD4-IgG1) were much less efficient when compared with mAb M-T413, particularly in blocking infection by fresh HIV-1 isolates. Also cellular transmission of HIV, as determined by syncytia formation within 24 hr, was prevented by mAb M-T413 when added within 45 min of contact of infected H9 cells with uninfected C8166 cells. Together with the favorable clinical experience obtained with CD4 mAbs as immunomodulatory drugs, these data suggest that infusion of CD4 mAb M-T413 may be a therapeutic modus for immediate prophylactic intervention after occupational exposure to HIV and for prevention of intrapartum mother-to-infant HIV transmission.**

Infectious uptake of human immunodeficiency virus (HIV) into cells is a complex process initiated by a specific high-affinity contact between the virus envelope glycoprotein gp120 and the cellular CD4 receptor (1–3). After binding to CD4, HIV enters the cell by a pH-independent fusion of the virus envelope with the cell membrane (4). The time interval between primary binding of HIV to CD4 and the irreversible fusion with the cell membrane is still unknown. Soluble CD4 (sCD4) as well as neutralizing antibodies specific for the hypervariable V3 loop of gp120 have been shown to inhibit infection *in vitro* even after attachment of HIV to CD4 (5, 6). We were interested in determining the period of time during which HIV remains sensitive to neutralization after its initial contact with a cell and in identifying the most appropriate postbinding inhibitors of infection. Such knowledge is critical for situations in which the time point of possible infection is known—for example, after occupational exposure to HIV by accidental needlesticks or other hazardous injuries with HIV-infected material. An effective postexposure prophylaxis of HIV infection is not yet known. Good candidates for postexposure intervention are agents that interfere with the gp120-CD4 binding, such as monoclonal CD4 antibodies (CD4 mAbs) or preparations of soluble CD4, because this interaction is mediated by structures highly conserved among a wide range of different HIV strains.

Here we show that HIV infection of cells can be prevented *in vitro* by the CD4 mAb M-T413 even when added as late as 30–120 min after cellular contact with virus. This antibody has been selected from a large panel of CD4 mAbs and proved to be far more effective than sCD4, particularly when postbinding inhibition of infection with primary HIV isolates was tested. Extensive clinical experience with murine and chimeric human/mouse CD4 antibodies has shown that treatment with these antibodies has no serious side effects. Thus, CD4 mAb M-T413 may be a useful tool for immediate intervention after occupational exposure to HIV and for prevention of mother-to-infant transmission of HIV during delivery.

MATERIAL AND METHODS

mAbs and Recombinant sCD4. The CD4 mAb M-T413 was selected from a panel of 110 different mAbs in our laboratory against the human CD4 molecule (7). It binds to the CD4V1 domain with an affinity of 8.6 $M^{-1} \times 10^{-9}$. Among all CD4 mAbs tested, it proved to be the most potent inhibitor of gp120 binding, HIV infection, and HIV-induced syncytia formation. In some experiments M-T426 (CD4V3/4-specific) was included as a negative control. mAbs were purified by preparative electrophoresis of concentrated hybridoma supernatant followed by gel chromatography on Sephacryl S-200 (Pharmacia). Monovalent Fab fragments were prepared by digestion of purified IgG preparations with immobilized papain (Pierce Europe, Oud-Beijerland, The Netherlands) and separation on protein G.

Recombinant sCD4 consisting of the four extracellular CD4 domains is secreted by the cell line CHO.T4.120.13 (Celltech, Slough, U.K.), which was kindly provided by A. N. Barclay (Oxford). sCD4 was purified from the supernatant by affinity chromatography on a CD4-mAb Sepharose column.

A hybrid CD4-human IgG1 construct (CD4-IgG1) was kindly provided by A. Traunecker (Basel, Switzerland) (8).

Cell Lines. The human T-cell line H9 was obtained from R. C. Gallo (National Institutes of Health); the T-cell line C8166 was provided by R. A. Weiss (London). Cells were cultured in RPMI 1640 medium containing 5% (vol/vol) fetal

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Abbreviations: sCD4, soluble CD4; CD4 mAb, monoclonal CD4 antibody; HIV-1 and HIV-2, human immunodeficiency virus type 1 and type 2; gp120 and gp41, HIV envelope glycoprotein gp120 and gp41; $TCID_{50}$, median infectious dose in tissue culture; FITC, fluorescein isothiocyanate.

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calf serum (Biochrom, Berlin) supplemented with 100 units of penicillin per ml and 50 μg of streptomycin per ml (GIBCO).

HIV Isolates. The HTLV-IIIB isolate was made available by R. C. Gallo. The monocytotropic HIV-1 isolate HIV1D117III (9) was obtained from H. Rübsamen-Waigmann (Frankfurt). All other HIV isolates were prepared by one of us (L.G.). MVP-899 is a HIV-1 laboratory strain isolated from a German AIDS patient in 1987. The MVP-15132 strain is a HIV-2 laboratory strain derived from a German patient in 1988 and is available through the National Institutes of Health Reagent Program. Primary HIV-1 isolates were obtained by cocultivating blood mononuclear cells from AIDS patients with alloantigen-stimulated blood mononuclear cells from healthy donors. Isolate MVP-6683 was derived from a patient in Germany, MVP-5180 is a HIV-1 variant from a patient in Cameroon, and MVP-9802 originates from a patient in Uganda. For *in vitro* infectivity tests, primary virus isolates were used immediately after adaption to H9 cells.

Soluble gp120. Purified soluble gp120 and the cell line 17.1 secreting recombinant HIV gp120 originate from Celltech (Slough, U.K.) and were made available by H. C. Holmes (Medical Research Council, AIDS Directed Programme, Potters Bar, U.K.).

Preparation of Mononuclear Blood Cells and Isolation of Blood Monocytes. Mononuclear blood cells were prepared by Ficoll/Hypaque (Pharmacia) density centrifugation of buffy coat cells from healthy volunteer donors. T lymphocytes were isolated using a direct mAb rosetting technique as described (10). Monocytes were cultured on hydrophobic membranes (Teflon) as described (9).

Infectivity Assays. Prior to infectivity assays the median infectious dose in tissue culture ($TCID_{50}$) was determined for each virus/target cell combination. The $TCID_{50}$ is defined as the reciprocal of the dilution at which 50% of the cultures are positive for virus. A control titration was included in each infectivity assay.

Short-Term Infectivity Assay. C8166 cells (3×10^4) were incubated with 1000 $TCID_{50}$ of different virus isolates in 100 μl of culture medium in microtiter plates (Tecnomara, Fernwald, F.R.G). For testing the capacity of CD4 mAb or sCD4 preparations to inhibit HIV infection, C8166 cells were treated for 30 min with various concentrations of CD4 mAb prior to virus addition or the HIVs were preincubated for 30 min with the CD4 constructs at various concentrations. Ten cultures were made at each concentration. Infection was evaluated after 6 days by monitoring syncytia formation.

Long-Term Infectivity Assay. Cells [3×10^5 per well of a 24-well plate (Tecnomara)] were incubated with 100 or 1000 $TCID_{50}$ of virus isolate. Inhibitors were added either prior to or after exposure to virus and were present for 14 days of culture. After 14 days cells contained in one well were washed four times with 10 ml of medium in a 10-ml tube and then cultured for an additional 20 days in the absence of inhibitors. Infection of cultures was evaluated by four methods in parallel: determination of infectious virus titer in the supernatant, syncytia formation assay, quantitation of the p24 core antigen levels in the supernatants using an ELISA Ag capture assay (DuPont), and detection of HIV DNA using the PCR amplification technique. All methods gave consistent results. For the sake of clarity only data obtained with the PCR and the p24 antigen determination are given.

Syncytia Formation Assay. H9 cells (1×10^5) were infected with 10,000 $TCID_{50}$ of HIV. After 3 days cells were extensively washed and mixed with 2×10^5 uninfected C8166 cells in 100 μl in microtiter plates, centrifuged for 1 min at 400 × *g*, and incubated at 37°C. To test inhibition of syncytia formation either cells were incubated with the respective inhibitor 30 min prior to mixing or inhibitors were added at various times after mixing the cells. Formation of syncytia was evaluated 24 hr later.

Measurement of HIV and HIV-gp120 Binding to Blood T Lymphocytes. Purified blood T lymphocytes (1×10^6) were incubated with 1×10^8 $TCID_{50}$ of the HIV-1 isolate MVP-899 in 1 ml of culture medium for 1 hr at 4°C. After three washings bound virions were detected by a polyvalent antiserum with double reactivity to HIV-1 and HIV-2 obtained from a healthy African donor followed by fluorescein isothiocyanate (FITC)-labeled polyvalent anti-human IgG antibody (Dianova, Hamburg, F.R.G.). Blood lymphocytes were incubated with a saturating concentration of soluble gp120 for 1 hr at 4°C. Bound gp120 was detected by the biotinylated monoclonal anti-gp120 antibody anti-env 108 (kindly provided by D. Healey, London) followed by staining with FITC-labeled avidin (Dianova). Fluorescence intensity of single cells was determined by cytofluorographic analysis using a FACScan (Becton Dickinson).

RESULTS

Inhibition of HIV Infection After Initial Binding of Virus. The exact time required for infectious cellular penetration by HIV is still unknown. We wondered whether cellular infection could be inhibited at a point of time when the virus had already bound to CD4. Of particular interest were substances that interfere with the gp120–CD4 interaction, such as CD4 mAb and soluble CD4, because the CD4 binding site on gp120 is conserved among a wide variety of HIV strains. To this end, H9 cells were incubated with either 100 or 1000 $TCID_{50}$ of the HIV-1 strain MVP-899. After various periods of time the CD4 mAb M-T413 and sCD4 were added, each at a concentration of 10 μg/ml. The cells were cultivated for 14 days in the presence of inhibitors. Subsequently, the cells were washed thoroughly and incubated for an additional 20 days. Finally, infection of cultures was simultaneously evaluated by four different methods. Previous experiments had shown a contact time of <5 min between 100 $TCID_{50}$ of HIV and susceptible cells to be required for infection (data not shown). Table 1 gives the inhibition data obtained for the infection with 1000 $TCID_{50}$. The CD4 mAb M-T413 prevented infection when applied within 30 min after cellular contact with virus. The monovalent Fab fragment of this antibody could also block infectious uptake of virus when given within 15 min after initial viral binding. The same efficiency in postbinding inhibition was obtained with monovalent recombinant sCD4.

The capacity of mAb M-T413 to inhibit infection after initial binding of virus was not restricted to the HIV-1 isolate MVP-899 and H9 cells. As shown in Table 1, infection of freshly isolated blood monocytes by 1000 $TCID_{50}$ of the monocytotropic HIV-1 strain D117III was prevented when the antibody was added within 60 min following initial contact with virus. The pattern of postbinding neutralization of the HIV-2 isolate MVP-15132 by mAb M-T413 was similar to the one obtained with the HIV-1 strain MVP-899. In this experiment sCD4 proved to be as efficient as the CD4 mAb. Results with other established HIV-1 laboratory strains such as HIV-IIIB were much like those obtained with MVP-899 (data not shown).

Inhibition of Infection with Primary HIV-1 Isolates After Initial Binding of Virus. Therapeutic trials as well as *in vitro* studies with recombinant constructs of sCD4 revealed that primary HIV-1 isolates required much higher doses of inhibitor for neutralization than laboratory strains (11). It was therefore of interest to compare the neutralizing capacity of sCD4 and mAb M-T413 before and after binding of primary HIV-1 isolates to susceptible cells. In a first set of experiments three different primary HIV-1 isolates obtained from patients from Germany, Cameroon, and Uganda were preincubated with different concentrations of monomeric and dimeric sCD4 constructs and then added to C8166 cells. The

Table 1. Postbinding inhibition of *in vitro* infection by various laboratory strains and primary isolates of HIV achieved with CD4 mAb M-T413 and sCD4

Postbinding interval, min	Laboratory HIV strain						Primary HIV isolate					
	MVP-899 (HIV-1)			D117III (HIV-1)	MVP-15132 (HIV-2)		MVP-6683 (HIV-1)		MVP-5180 (HIV-1)		MVP-9802 (HIV-1)	
	M-T413											
	IgG	Fab	sCD4	M-T413	M-T413	sCD4	M-T413	sCD4	M-T413	sCD4	M-T413	sCD4
0	−	−	−	−	−	−	−	+	−	+	−	+
15	−	−	−	−	−	−	−	+	−	+	−	+
30	−	+	+	−	−	−	−	+	−	+	−	+
60	+	+	+	−	+	+	−	+	−	+	−	+
120	+	+	+	+	+	+	−	+	−	+	−	+

Cells (3×10^5) were incubated with 1000 $TCID_{50}$ of HIV isolate at 37°C. Monocytotropic HIV-1 isolate D117III was tested on blood monocytes; all other HIV isolates were analyzed on H9 cells. At the times indicated CD4 mAb M-T413 or sCD4 was added at a final concentration of 10 μg/ml. At day 14 cells were washed four times. After an additional 20 days of culture in the absence of inhibitor, infection of cells was determined. +, Positive PCR and >1000 pg of HIV p24 antigen per ml in the supernatant as measured by the p24 ELISA; −, negative PCR and HIV p24 antigen in the supernatant below the detection level of the p24 ELISA (<12 pg/ml).

laboratory strain MVP-899 was included as a control. The inhibitory capacity of M-T413 was tested by preincubation of C8166 cells with different antibody concentrations followed by exposure to primary HIV isolates. Fig. 1 shows the results obtained in a short-term infectivity assay. Both sCD4 preparations were 10-fold less effective than the CD4 antibody in preventing infection by the laboratory strain MVP-899. However, they were 300–1000 times less effective in inhibiting infection by the primary HIV isolates. This difference in the ability to neutralize fresh HIV isolates became even more evident when postbinding neutralization was tested. As shown in Table 1, infection with 1000 $TCID_{50}$ of all three primary isolates was blocked by the CD4 mAb even when added 120 min after cellular exposure to virus. sCD4, however, was not able to neutralize even when it was applied immediately after virus addition.

Dissociation of CD4-Bound gp120 or Complete HIV Particles by CD4 mAb M-T413. One possible explanation for the antibody's remarkable activity in postbinding neutralization may be its capability to displace the bound virus from CD4. To test this possibility experiments were carried out in which the displacement of gp120 as well as of complete virions from the cells by mAb M-T413 was followed. To this end peripheral blood lymphocytes or purified blood T cells were incubated with either recombinant soluble gp120 at saturation conditions (Fig. 2*a*) or with 1×10^8 $TCID_{50}$ of the HIV-1 isolate MVP-899 (Fig. 2*b*) for 1 hr on ice. Unbound soluble gp120 and virions were then removed by washing and M-T413 was added at concentrations of 10 and 100 μg/ml. After various periods of time cells were stained for bound gp120 or virions and quantitatively analyzed by cytofluorography. As shown by Fig. 2*a*, with 10 μg of mAb M-T413 per ml, a slight reduction of bound gp120 was obtained only after 180 min. With 100 μg/ml, the decline was more pronounced after 180 min but was far from being complete. In contrast to monovalent gp120, bound virions were not displaced by M-T413 after 90 min even at the high concentration of 100 μg/ml (Fig.

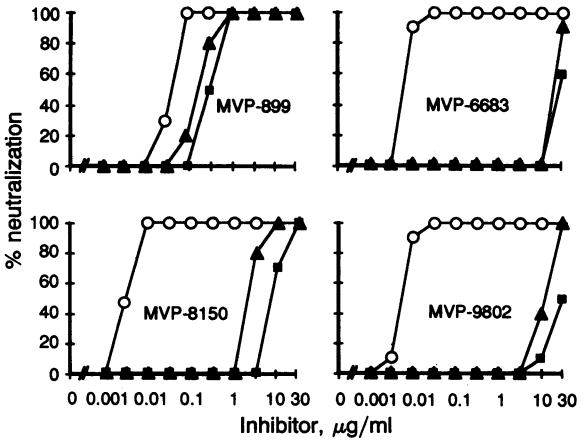

FIG. 1. Capacity of CD4 mAb M-T413, sCD4, and sCD4-IgG1 to inhibit infection of C8166 cells by primary HIV-1 isolates. C8166 cells were preincubated with various concentrations of CD4 mAb M-T413; HIV isolates were preincubated with various concentrations of sCD4 and sCD4-IgG1. Then 1000 $TCID_{50}$ of virus isolate was added to 3×10^5 cells. For each inhibitor concentration 10 different cultures were set up. After 6 days the frequency of infected cultures was evaluated by determining the formation of syncytia. Percent neutralization was defined as 100% minus % infected cultures and plotted against the concentration of inhibitor. ○, CD4 mAb M-T413; ■, sCD4; ▲, sCD4-IgG1.

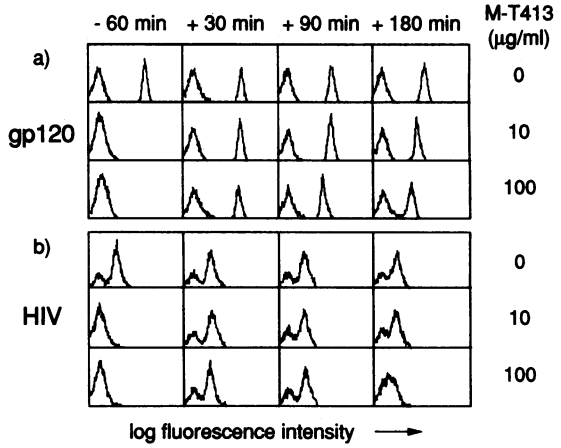

FIG. 2. Dissociation of CD4-bound recombinant gp120 and HIV virions by CD4 mAb M-T413. (*a*) Peripheral blood lymphocytes were incubated with a saturating amount of recombinant soluble HIV gp120 for 1 hr on ice. CD4 mAb M-T413 was then added to final concentrations of 10 and 100 μg/ml. After the times indicated, bound gp120 was detected by a biotinylated monoclonal anti-gp120 antibody followed by FITC-labeled avidin. Analysis by fluorocytometry is displayed as a single histogram. As a control, the CD4 antibody was added simultaneously with the gp120, as indicated by the −60-min interval. (*b*) Purified blood T cells were incubated with 1×10^8 $TCID_{50}$ of the HIV-1 isolate MVP-899 for 1 hr on ice. CD4 mAb M-T413 was then added to final concentrations of 10 and 100 μg/ml. After the times indicated, bound virus was detected by a polyvalent anti-HIV antiserum followed by a FITC-labeled anti-human IgG antibody. Analysis by fluorocytometry is displayed as a single histogram. As a control, the CD4 antibody was added simultaneously with the virus as indicated by the −60-min interval.

2*b*). Only after 180 min of incubation a reduction in the number of cell-bound virions was detectable. At the concentration of 10 μg of M-T413 per ml, effective for postbinding blockade of infection, no displacement of bound virions was observed even after 180 min. When the antibody was added simultaneously with gp120 or virus, complete inhibition of binding of gp120 and HIV virions was achieved, as shown by the −60-min histograms. These results clearly show that postbinding neutralization by CD4 mAb M-T413 at 10 μg/ml cannot be explained by mere displacement of virions from cellular CD4.

Inhibition of Syncytia Formation by Delayed Addition of CD4 mAb or sCD4. In addition to infection by free HIV, cells are also infected by cell-to-cell transmission of virus through membrane contact with infected cells. To determine whether also cell-mediated viral transmission could be prevented by delayed addition of CD4 mAb or sCD4, experiments were designed in which syncytia formation between infected H9 cells and uninfected C8166 cells within 24 hr was used as an indicator of cellular virus transmission. Control experiments revealed that free virus produced by the infected H9 cells within 24 hr did not induce syncytia formation in C8166 cells before 48 hr. Contact between cells was facilitated by a short centrifugation after mixing. As shown in Table 2, mAb M-T413 was capable of blocking syncytia formation when added within 45 min after contact between infected and uninfected cells, whereas the CD4V3/4-specific mAb M-T426 was ineffective. The soluble CD4 constructs were much less efficient in this respect than the CD4 mAb. For prevention of syncytia formation, monomeric sCD4 had to be introduced immediately after mixing of cells and addition of the more potent dimeric CD4-IgG was required within 10 min.

DISCUSSION

The main interacting site of CD4 with gp120 could be localized in a particular peptide loop in the CD4V1 domain that is homologous to the complementarity-determining region 2 of the variable immunoglobulin light chain domain (12). CD4 mAbs recognizing this structure have proved to be extraordinarily potent in blocking HIV infectivity. Detailed analysis of 110 different CD4 mAbs led to the selection of the CD4V1-directed mAb M-T413 displaying a peculiar activity to inhibit HIV infectivity, which was also apparent when the virus was added to susceptible cells with a head start of 30–60 min. This postbinding inhibition clearly warranted a more detailed study because in several therapeutic trials anti-CD4 antibodies have proved to be very potent nontoxic agents for blocking and eliminating CD4+ T cells (13, 14). They therefore appeared as prime candidates to prevent infection after exposure to HIV through an accidental injury with HIV. For comparison, preparations of sCD4 were tested as additional substances interfering with the gp120–CD4 interaction.

Table 2. Inhibition of syncytia formation by delayed addition of CD4 mAb or sCD4

Interval,* min	Inhibitor			
	M-T413	M-T426	sCD4	CD4-IgG1
0	0	+++	0	0
10	0	+++	++	0
30	0	+++	+++	+
45	0	+++	+++	+++
60	+	+++	+++	+++
120	++	+++	+++	+++

H9 cells infected 3 days previously with 10,000 $TCID_{50}$ of HIV-1 isolate MVP-899 were mixed with uninfected C8166 cells. At the times indicated, inhibitors were added at a concentration of 10 μg/ml. All cultures were set up as triplicates. Twenty-four hours later the formation of syncytia was evaluated and scored as follows: 0, no syncytia found; +, at least one syncytium detected in one of three wells; ++, ≤30 syncytia per well; +++, >30 syncytia per well.

*Interval between mixing of cells and addition of inhibitor.

To establish virus clearance from cultures, evaluation at day 30 after virus exposure was judged to be appropriate. For this analysis four different methods were applied simultaneously, which gave consistent results.

Aside from the critical role of the type of inhibitor, postbinding blocking of infection was mainly dependent on the type of target cell and on the virus strain. In a large series of experiments postbinding neutralization by mAb M-T413 and sCD4 was demonstrated using combinations of different HIV isolates and various cell types. A striking difference between mAb M-T413 and sCD4 was revealed when primary HIV isolates were tested. This study confirms the reported resistance of primary HIV isolates to sCD4 treatment (11) and demonstrates the peculiar efficacy of mAb M-T413 in neutralizing fresh isolates and laboratory strains (Fig. 1). The different sensitivity of primary HIV-1 isolates to CD4 mAb compared with sCD4 was particularly evident in the postbinding inhibition of infection (Table 1). Whereas infection by all three primary isolates originating from widely dispersed geographical regions could be inhibited by mAb M-T413 when added as late as 120 min after virus contact, sCD4 failed to block infection at a concentration of 10 μg/ml even when given simultaneously with virus. Since soluble gp120s derived from primary clinical HIV-1 isolates have CD4-binding affinities similar to those of gp120s derived from laboratory strains (15), the different sensitivity to neutralization by sCD4 may depend upon the altered accessibility of CD4-binding sites on the gp120/gp41 complex in the intact viral membrane (3).

The mechanism by which delayed addition of CD4 mAb or sCD4 prevents infection of cells is still elusive. Previous experiments revealed that repeated washings of cells by centrifugation immediately after virus–cell interaction could not prevent infection. This was shown for all combinations of target cells and virus strains investigated in this study (data not shown). Thus, only a short contact time between virus and cell membrane is required for effective binding. Therefore, inhibition of infection seen after delayed addition of CD4 mAb or sCD4 cannot be caused by blocking initial CD4-gp120 binding. On the other hand, when gp120 or HIV virions were allowed to bind to cellular CD4 for 1 hr, mAb M-T413 was not able to displace gp120 or HIV virions from CD4 at a concentration of 10 μg/ml within 90 min. For this reason, postbinding inhibition of infection cannot be explained by removal of CD4-bound virus.

A likely explanation for the striking capacity of CD4 mAb M-T413 to prevent HIV infection at a postbinding step is the interference with conformational rearrangements of the CD4-gp120/gp41 complex or with a cooperative recruitment of additional gp120–CD4 interactions required for viral fusion with the cell membrane (3, 16). Since also the monovalent Fab fragment of M-T413 was effective, crosslinking of CD4 molecules seems not to be essential for postbinding inhibition of infection. In kinetic studies Orloff *et al.* (17) have shown that HIV requires a binding time of at least 30 min at 37°C for productive infection.

The virus dose of 1000 $TCID_{50}$ used here corresponds to virus titers found in 100–200 μl of plasma from patients with AIDS or AIDS-related complex or suffering from acute HIV-1 infection (18, 19). Since infection with this dose of primary HIV-1 isolates can be inhibited *in vitro* by the CD4 mAb M-T413, even when added as late as 2 hr after exposure to virus (Table 1), a therapeutic potential of CD4 mAb treatment after occupational exposure to HIV may be considered. The postexposure use of CD4 mAb is also warranted

by the observation that transmission of virus from infected cells is blocked by delayed addition of CD4 mAb in the syncytia formation assay (Table 2). The finding that administration of CD4-IgG can prevent infection of chimpanzees with the laboratory strain HIV-1 IIIB indicates that substances interfering with the CD4–gp120 interaction are basically capable of inhibiting HIV infection *in vivo* (20). Another important indication of CD4 mAb treatment could be the HIV transmission from infected mothers to children. Recent reports suggest that a substantial part of mother-to-infant transmission occurs close to or at delivery (21, 22). As demonstrated in >150 patients with various autoimmune diseases, treatment with CD4 mAb is a well-tolerated and safe therapeutic procedure (refs. 13, 14, 23; unpublished observation). In addition, neutralizing serum concentrations of at least 10 μg/ml can be obtained within 30 min of the infusion of 100 mg of CD4 antibody (unpublished observation). $CD4^+$ T cells are removed from the circulation to >90% within 2–3 hr after infusion, thus reducing circulating target cells for HIV infection (13). An additional positive effect of CD4 mAb administration might be seen in the inhibition of T-cell activation that is required for complete reverse transcription (24) or virus integration (25). A primate model simulating the conditions of accidental exposure can be explored since several primate species show extensive cross-reactivity with mAbs against human CD4 (26).

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