

# The Interaction of Macrophage and Non-Macrophage Tropic Isolates of HIV-1 with Thymic and Tonsillar Dendritic Cells in Vitro

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## Summary

Dendritic cells isolated from thymus and tonsil were tested for susceptibility to HIV-1 strains that are tropic for macrophages or for T cell lines. DCs were purified by cell sorting and before infection expressed high levels of CD4 and HLA-DR and lacked markers for T, B, NK cells, or macrophages. Viral entry and reverse transcription was found after pulsing with strains of HIV-1 that could infect macrophages. During the first 36 h the PCR signals for gag sequences increased in DCs and macrophages. In contrast little if any viral DNA was found after pulsing macrophages or DCs with HIV-1 that was able to infect T cell lines. DCs pulsed with HIV-1 were able to transmit infection to responding T cells during an allogeneic or superantigen response.

Selection for virus able to infect lymphoid DCs and other DCs expressing CD4 and its transfer to T cells during subsequent immune responses may provide a mechanism for the observed predominance of macrophage-tropic HIV-1 after in vivo transmission.

Dendritic cells (DCs)<sup>1</sup> are leukocytes specialized for antigen processing and presentation to T cells (1). Abnormalities of antigen presentation that may be attributable to dysfunction of DCs have been reported in HIV-1-infected individuals (2–4). Such abnormalities increase during the course of the disease, but it remains unclear whether these changes are directly due to infection of the DCs (5) or to indirect viral effects that are independent of DC infection. Defective proliferative responses during the cognate interaction of T cells with virus-pulsed DCs (6) occurs, but frequent infection of the DCs is not required (7).

Estimates of virus susceptibility of isolated DCs and Langerhans cells (LCs) have varied widely. Productive infection has been reported in some but not all the studies of blood DCs (6, 8–13) although cultured DC-enriched populations rather than purified DCs have often been used. Differences in the DC phenotype and the composition of the DC-enriched fraction used as targets, in particular differences in CD4 expression, may explain differences in HIV-1 susceptibility. The reduced density of cultured blood DCs facilitates enrichment (14–16), but cultured

blood DCs express little if any CD4 (8, 16). Two populations of fresh blood DCs strongly express CD4 (17, 18), but after culture and functional maturation CD4 is lost (16, 17).

To better define the role of CD4 and the extent of HIV-1 entry into DCs from sites in which immune responses occur in vivo we examined the susceptibility of sorted DCs from lymphoid tissue. Cultured tonsil DCs are potent antigen-presenting cells (APCs) (19, 20) that express costimulator molecules (20) and continue to express CD4 in culture (19). Functionally they resemble cultured blood DCs (16). Thymic cells isolated directly without culture express high levels of CD4 and function as potent APCs (21, 22). We now show that the functionally mature CD4<sup>+</sup> lymphoid DCs from both tonsil and thymus can be infected by HIV-1, but there is preferential entry of virus that is able to infect macrophages.

## Materials and Methods

*Isolation of Primary Cells.* Thymic DCs were obtained using the method of Winkel et al. (22). Human thymus (neonatal–11 yr) discarded during cardiac surgery was used. Thymus was stored on ice during transport and was processed the same day (usually within 8 h). Tissue was carefully dissected, suspended in 15 ml RPMI-1640 (+2% FCS) containing 2 mg/ml collagenase (type II; Worthington Biochemicals, Freehold, NJ) and 0.02 mg/ml

<sup>1</sup>Abbreviations used in this paper: DC, dendritic cells; RT, reverse transcriptase; SI, Syncytia inducing; NSI, non-syncytia inducing; MOI, multiplicity of infection; NHS, normal human serum.

DNase I (grade II bovine pancreatic DNase I; Boehringer Mannheim, Mannheim, Germany) and digested for 20–30 min at 22°C. 1.5 ml EDTA (100 mM, pH 7.2) was added for 5 min and cells were filtered through a steel sieve (80–100 gauge; Swiss screens, Sydney, Australia). Cells were pelleted, suspended in isotonic metrizamide ( $d = 1.065$  g/ml), and run over a metrizamide cushion ( $d = 1.065$ ) at 1600  $g$  for 10 min at 4°C. Low density cells expressing CD2, 3, 14, and 19 were removed by labeling with monoclonal antibodies and two rounds of depletion with magnetic beads (GAM-coated paramagnetic beads; Dynal, Oslo, Norway). The residual cells were labeled with FITC-conjugated HLA-DR and cells with high and intermediate expression of HLA-DR sorted as two separate populations using a FACStar plus (Becton Dickinson, Mountain View, CA).

Tonsils dendritic cells were obtained using modifications of the method described by Hart and McKenzie (19). Normal human serum (NHS) was used throughout the isolation, and T cells were not specifically removed before culture. Tonsils were stored on ice in medium containing 250  $\mu$ g/ml gentamicin and processed within 3 h. The epithelial layer was removed and tissue dissected and digested in medium containing 0.5 mg/ml collagenase (type II; Worthington) and 5  $\mu$ g/ml DNase I (Boehringer Mannheim, Mannheim, Germany) for 20 min at 37°C. EDTA was added for 5 min and cells pelleted and resuspended in isotonic metrizamide and then run on a density columns at 1600  $g$  for 10 min at 4°C. Cells with a density between 1.040 and 1.065 were collected and washed before culture at  $3\text{--}5 \times 10^6$ /ml in R10 NHS (RPMI 1640, gentamicin 25  $\mu$ g/ml, glutamine 2 mM, 2 ME 0.025 mM, Hepes 10 mM, 10% NHS) for 36–40 h. HLA-DR<sup>+</sup> cells negative for lineage markers (CD3, 14, 19, and 56) were contained in the low density fraction. Low density cells were collected over a second metrizamide gradient and labeled with optimal concentrations of hybridoma supernatants to CD3 (OKT3), CD19 (FMC63), CD14 (3C10), and CD11b (OKM1). Cells were panned twice on dishes coated with sheep anti-mouse Ig antibody (SAM; Silenus, Melbourne, Victoria, Australia) at 5  $\mu$ g/ml. The nonadherent cells from the antibody pans were labeled with PE conjugated SAM (Silenus) and large PE-negative cells sorted on a FACStar Plus (Becton Dickinson).

Monocyte derived macrophages were plastic adherent cells cultured for 5–7 d in 10% human serum. Cells were cultured in R10 NHS in teflon dishes (Sarillex, Minnetonka, MN). Before infection cells were plated in fresh medium for 0.5–1 h and any residual non-adherent cells were removed.

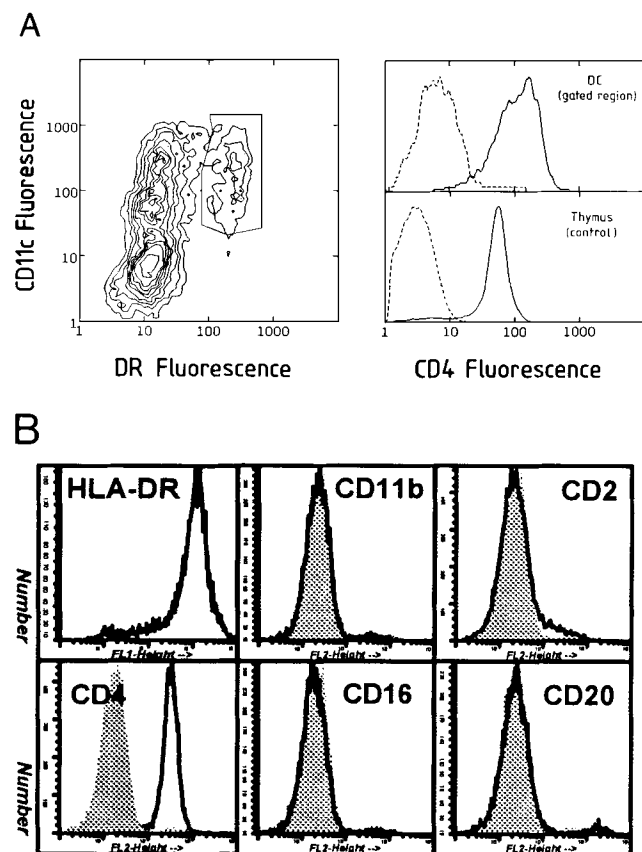
CD4<sup>+</sup> T cells were purified from elutriated lymphocytes or the Er<sup>+</sup> fraction of buffy coats by negative selection using hybridoma supernatants to CD8 (OKT8), CD19 (FMC63), and HLA-DR (FMC 52) and panning on SAM-coated plates.

The T cell lines CEM-T4, MT-2, and the cell line 8E5 that contains a single defective copy of HIV-1 per cell, were grown in R10 FCS and passaged twice weekly. Cell lines were obtained through the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH.

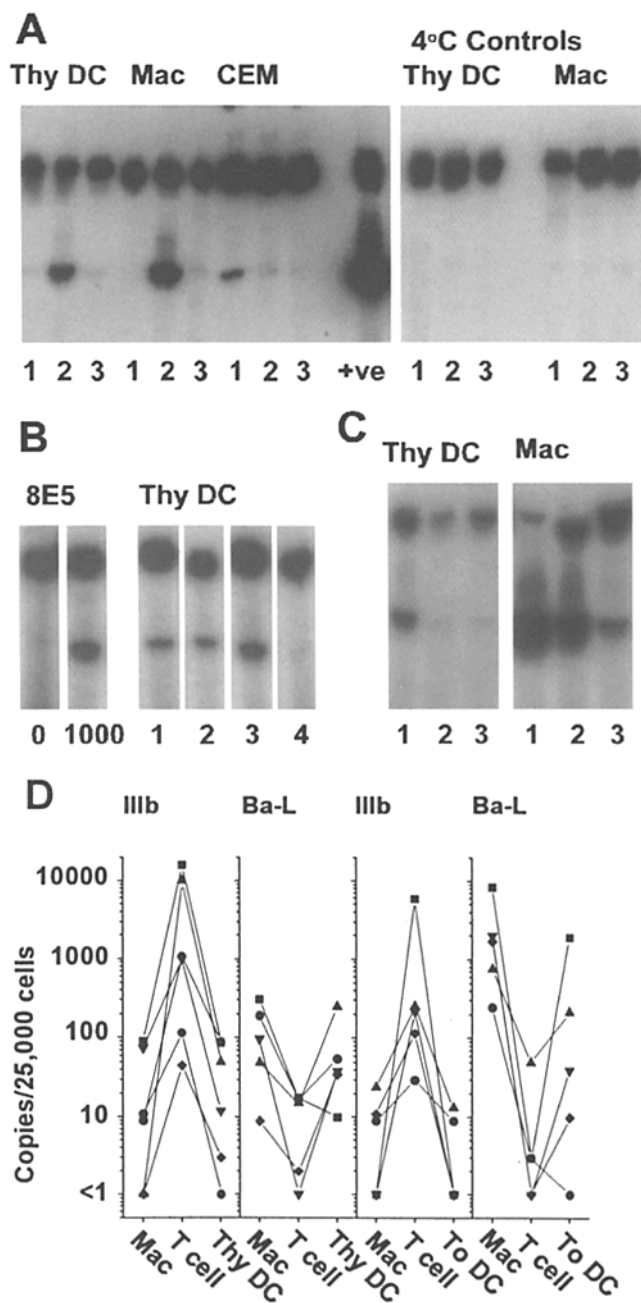
**Virus Culture and Infection.** Low passage patient isolates 228 (syncytium-inducing [SI] phenotype in MT-2 cells) and 676 (non-syncytium-inducing [NSI] in MT-2 cells), the T cell line tropic virus IIIb and the macrophage-tropic virus Ba-L were grown in mitogen activated PBMCs. Isolates IIIb and 228 were also grown in CEM-T4 or MT-2, and Bal and 676 in cultured macrophages. Virus stocks were stored at  $-70^\circ\text{C}$ , and treated with RNase free DNase I (50 U/ml, Boehringer Mannheim, Mannheim Germany) for 20 min at 22°C and filtered (0.2- $\mu$ m filter) before use.

Target cells were exposed to HIV-1 viral supernatants for 1.5–2 h at 37°C, washed and cultured in T cell conditioned medium. Multiplicities of infection (MOIs) were between 0.01 and 0.1. For PCR, cells ( $50\text{--}100 \times 10^3$  cells per well) were pulsed with HIV-1 in microtiter plates for 1.5 h at 37°C, washed once, and then cultured in 30% T cell conditioned medium. Cell lysates were harvested after 24–36 h. For transfer experiments DCs were pulsed with HIV-1 in eppendorf tubes for 1.5–2 h before washing four times with medium. Washed cells were added to allogeneic T cells ( $10^4$  DCs to  $1\text{--}1.5 \times 10^5$  CD4<sup>+</sup> T cells) immediately or after 24 h culture in T cell-conditioned medium. The mixed leukocyte reactions (MLRs) were performed in triplicate in flat-bottomed microtiter plates in R10 NHS. Supernatants for RT analysis were harvested and stored at  $-70^\circ\text{C}$ .

For AZT blocking the target cells were incubated in medium containing 30  $\mu$ M AZT for 3 h before pulsing with virus super-



**Figure 1.** Strongly HLA-DR-positive sorted thymic and tonsil DCs express high levels of CD4. (A) Low-density thymic cells depleted of contaminating cells by immunomagnetic bead depletion using CD14, 3, 2, and 19 were sorted into DR<sup>hi</sup> and DR<sup>lo</sup> cells. DR<sup>hi</sup> cells (Thymic DCs) expressed CD11c and had a typical DC morphology. DR<sup>lo</sup> cells were heterogeneous for expression of CD11c. Total DR<sup>lo</sup> and the two subpopulations defined by CD11c were tested for susceptibility to HIV-1 (DR<sup>lo</sup> cells, Figs. 2, 3). The thymic DCs (and DR<sup>lo</sup> cells) had similar CD4 expression to CD4<sup>+</sup> thymocytes. (B) Tonsil DCs expressed high levels of HLA-DR and CD4 but did not express lineage-specific markers. Low-density cultured tonsil cells were partially depleted of CD3-, 14-, and 19-bearing cells by panning. Cells were labeled with PE-SAM and the large null cells sorted. The collected cells were labeled with FITC conjugated HLA-DR alone or with PE-labeled CD2, CD20, CD11b, CD16, or CD4 (FL2).



**Figure 2.** Lymphoid DCs are preferentially infected by macrophage-tropic virus by CD4 dependent mechanisms. (A) Similar numbers of thymic DCs, cultured macrophages, and CEM were pulsed with IIIb (lane 1), Ba-L (lane 2), and YU-2 (lane 3). HIV-1 gag transcripts were detected by PCR after 36 h of culture. Positive control was  $10^4$  of the 8E5 cell line that carries one provirus per cell and negative controls were cells pulsed with virus at 4°C. HLA-DQA primers were included in each reaction to amplify genomic sequence (upper bands). (B) Both DR<sup>lo</sup> (lanes 1 and 2) and DR<sup>hi</sup> (lane 3) thymic DCs were susceptible to virus entry by macrophage tropic isolates. The thymic populations negative for lineage-specific markers were sorted for CD11c and HLA-DR. The DR<sup>lo</sup> CD11c<sup>-</sup> (lane 1), DR<sup>lo</sup> CD11c<sup>+</sup> (lane 2) and DR<sup>hi</sup> populations were all susceptible to NSI patient isolate 676. Entry into the thymic DCs (DR<sup>hi</sup>, lane 3) was blocked by sCD4 (lane 4). (C) HIV-1 Ba-L infection of thymic DCs (DR<sup>hi</sup>) was blocked by antibody to CD4 (lane 2, 5  $\mu$ g/ml) and by soluble CD4 (lane 3, 50  $\mu$ g/ml). Entry into macrophages was completely blocked under the same conditions. (D) Frequency of HIV-1 provirus in thymic DCs, tonsil DCs, macrophages, and T cell lines after a

nanat containing 30  $\mu$ M AZT. This dose blocked production of PCR gag template in T blasts, macrophages, and DCs.

**Reverse Transcriptase Assay.** Reverse transcriptase activity in supernatants was assayed as previously reported (7). Filters were counted in a microbeta counter with cross-talk correction (Wallac, Turku, Finland) with Meltilex scintillant (Wallac).

**Semiquantitative PCR.** PCR was performed as previously reported (7).

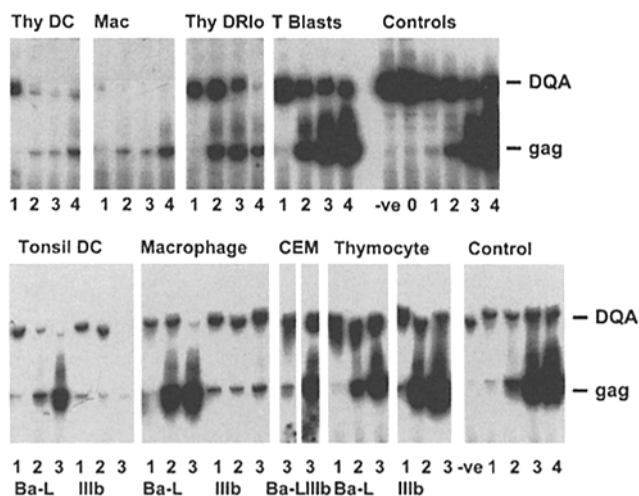
## Results and Discussion

**Phenotype and Infection of Lymphoid DCs and Subpopulations.** In contrast to most previous studies of isolated DCs we have used cells that express high levels of CD4. The phenotype and function of the DR<sup>hi</sup> thymic DCs have been reported (21). Within the DR<sup>lo</sup> population of lineage-negative thymic cells a residual subpopulation became plastic adherent, but the majority continued to express CD4, increased DR expression, and appeared by morphology to be DCs. After overnight culture a single DR<sup>hi</sup> population was found (data not shown) suggesting the DR<sup>lo</sup> cells mainly consists of a subpopulation of DCs. Although all the DR<sup>hi</sup> cells expressed CD11c, expression in the DR<sup>lo</sup> population was heterogeneous (Fig. 1 A). Most of the sorted tonsil cells enriched for DCs by sorting for the CD14<sup>-</sup>, CD3<sup>-</sup> CD19<sup>-</sup> large cells expressed high levels of HLA-DR and CD4 (Fig. 1 B) and did not express the markers CD2, 20, 16, and 11b, found on T, B, and NK cells, and macrophages. The DCs expressed CD80 (B7/BB1) but not CD11c, exhibited a typical dendritic morphology and rapidly formed aggregates of veiled cells (data not shown). In contrast CD11c<sup>-</sup> blood DCs were immature and required conditioned medium for maturation and survival and lost CD4 during culture (16, 17). Levels of CD4 at the time of infection were similar in the fresh thymic DCs, DR<sup>lo</sup> thymic cells, cultured tonsil DCs, and the T cells (Fig. 1, A and B).

Viral entry was easily detected by PCR. HIV-1 gag transcripts were present after the thymic DCs had been pulsed with Ba-L but not with the IIIb isolate (Fig. 2 A). Entry into the DCs was almost completely blocked by soluble CD4 and anti-CD4 antibody (Fig. 2, B and C). Within the DR<sup>lo</sup> thymic population both the CD11c<sup>+</sup> and CD11c<sup>-</sup> subpopulations were infected by macrophage tropic virus (Fig. 2 B), discounting macrophage contamination as an explanation. The number of copies of macrophage-tropic virus in DCs was usually less than in cultured macrophages (0.3–0.1) but almost invariably greater than in T cell lines (Fig. 2 D).

The tropism of HIV-1–infecting thymic DCs was of particular interest because a close developmental relationship to T cell has been shown in the mouse (23). However, this relationship does not extend to susceptibility to SI virus since thymic DCs were no more susceptible to the T cell

virus pulse. The number of copies was determined by densitometric comparison of gag signal in the semiquantitative PCR assay. Mac, cultured macrophages; T cell, CEM-T4 or MT2; ThyDC, thymic DC; toDC, tonsil DC.



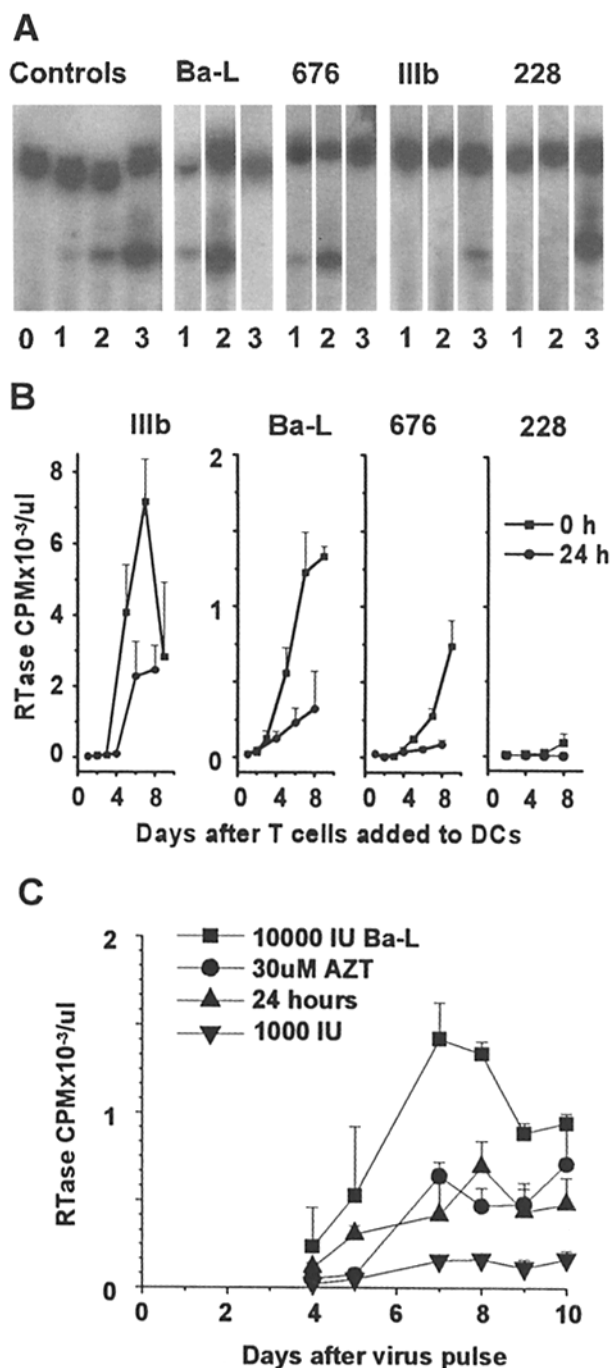
**Figure 3.** Macrophages, tonsil DCs, and thymic DCs show similar kinetics of viral entry and tropism. (A) Macrophages, Thymic DC and the DR<sup>lo</sup> sorted populations were pulsed with Ba-L and cell lysates harvested after different times in culture. 1 = 0, 2 = 12, 3 = 24, 4 = 48 h after virus pulse. Controls were PHA blasts. (B) Sorted tonsil DCs were pulsed with Ba-L and IIIb strains and infection compared to that in thymocytes, cultured macrophages, and the T cell line CEM. PCR for gag and DQA sequences was performed at the end of the pulse (0 h, lane 1) after 10 h (lane 2), and after 36 h (lane 3) of culture. Increased signal occurred in the Ba-L infected DCs and macrophages but not in IIIb-infected tonsil DCs. Controls were 8E5 cells (-ve = 0, 1 = 10, 2 = 100, 3 = 1000, 4 = 10000 copies of 8E5).

line-tropic strains of HIV-1 than macrophages using either DR<sup>hi</sup> DCs or the DR<sup>lo</sup> immature DCs as targets. Thymic and tonsil DCs were similar in HIV-1 susceptibility.

In sorted thymic DCs and permissive cells a PCR signal for gag was present after 10–12 h but not at the end of the pulse with Ba-L (1.5–2 h) (Fig. 3, top). The signal increased up to the endpoint of the analysis (48 h) and was comparable to the signal found with a similar number of Ba-L-infected macrophages.

Sorted tonsil DCs, pulsed with virus and analyzed by PCR showed efficient entry by Ba-L compared to IIIb (Fig. 3, bottom). With Ba-L, gag increased with time up to the endpoint (36 h), but little change in gag occurred in cultures pulsed with IIIb. Thymocytes were susceptible to HIV-1 as reported by others (24) and were infected by both isolates. The cell line CEM was infected to high levels only by the IIIb isolate. Infection of thymic DCs in vivo has been suggested by the observation of p24 antigen in cells with DC morphology in the implanted human thymus of SCID-hu-mice after infection with patient isolates of HIV-1 (24). Exogenous infection of thymic DC populations was also found (25) but the tropism of the infecting virus was not defined.

**HIV-1 Infection and Transfer from DCs to T Cells.** We have previously shown that cultured blood DCs, although infrequently infected, can carry virus and transmit infection to resting T cells during stimulation (6) or to T cell lines during coculture (26). Detectable viral entry into sorted tonsil DCs occurred with Ba-L and 676 but not by IIIb and 228



**Figure 4.** Both NSI and SI isolates of HIV-1 are transferred from virus-pulsed DCs to CD4<sup>+</sup> T cells but viral entry into DCs by NSI is greater. (A) Viral entry of macrophage-tropic virus but not T cell line tropic isolates into tonsil DCs was detected by PCR. Tonsil DCs (lane 1), macrophages (lane 2), and the T cell line MT2 (lane 3) were pulsed with virus and cultured for 36 h before PCR. (B) Virus production in cocultures of DCs pulsed with SI isolates (IIIb and 228) and macrophage-tropic NSI isolates (Ba-L and 676) was measured by RT. Triplicate cultures to which allogeneic T cells had been added immediately (0 h) were compared to cultures to which T cells were added after culturing the DCs after the virus pulse (24 h). (C) Transfer of Ba-L from virus-pulsed tonsil DCs was reduced if the DCs were cultured for 24 h before addition of T cells or if the DCs were preincubated with AZT (30  $\mu$ M for 3 h) and virus added in the presence of AZT. DCs pulsed with lower concentration of virus (1,000 TCID<sub>50</sub>) had reduced virus production.

strains (Fig. 4 A). However virus transmission to T cells in an MLR was found with all strains. After the virus-pulsed DCs were cultured for 24 h, transmission occurred, but RT production was reduced (Fig. 4 B). Proliferative responses (12 h [<sup>3</sup>H]thymidine uptake measured after 4 d) were decreased by <15% by 24 h of culture of DCs. Reduction of input virus and pretreatment with AZT also reduced but did not eliminate virus production in the cocultures (Fig. 4 C), suggesting that the infection of DCs was contributing to HIV-1 transmission, but carriage of virions as described for blood DCs (6, 12) also occurred. During the virus pulse tight aggregates of DCs formed. Sequestration of virions in these clusters may contribute to the ob-

served transmission but it is unclear if this would occur in vivo and contribute to virus carriage.

DCs and LCs process antigen peripherally and migrate to draining lymph nodes or spleen. In this study we have shown preferential entry of macrophage-tropic, NSI, virus into CD4 lymphoid DCs from thymus and tonsil. If CD4-expressing DCs from other sites exhibit a similar profile of susceptibility, preferential infection and carriage of macrophage-tropic virus from sites of HIV exposure to responding T cells in lymphoid tissue may explain the predominance of macrophage-tropic virus during the initial viraemia of HIV-1 (27).

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