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Ethical considerations to help assure high quality care in the global epidemic of AIDS

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The local and global presence of AIDS presents novel and very serious societal challenges unprecedented in our lifetimes. Any serious challenge threatens the usual ways a society conducts itself in order to preserve its most important values. Ethics is the analysis of basic conduct, character traits (virtues) and duties that are shared by a society, the goal being to set priorities and establish guidelines that will honor respect for human dignity while preserving other important societal values. Ethical analysis becomes especially relevant in crises situations such as the one the AIDS epidemic has imposed. Conduct, traits and duties often are incorporated into general ethical principles for purposes of analysis.

While it can be argued that societal values will vary from one group to another, it can be assumed that the basic value of good health is shared by all people. Health professionals are one societal resource for realizing that value, and their professional codes of ethics delineate principles that are shared across cultures and nations. In this presentation, ethical principles of beneficence and distributive justice are described to provide the starting point for an ethical analysis of three serious societal challenges due to the presence of HIV and its clinical manifestations in AIDS. These principles are general enough that any society can further specify how they are to be understood in its own specific cultural and social context. Principles of non-abandonment, participation and proportionality also are introduced.

The three challenges are: the tension between a patient's or family's desire to keep HIV status private and a third party's need to know; the tension between the professional's duty to obtain informed consent for testing or research and the urgency to provide treatment or find solutions to the ravages of the virus; and the tensions created for health professionals and patients by the presence of scarce resources to treat AIDS combined with negative societal attitudes regarding some infected groups. Each tension is analysed according to current ethical thinking in the USA and by major international bodies. In regards to the third challenge that addresses allocation of resources to treat HIV, key arguments in the debate about the moral responsibilities of health professionals in affluent societies such as Japan and the USA towards impoverished nations are included.

Drawing on these ethical analyses of how to help assure high quality health care for AIDS at local and international levels, the presentation concludes with several proposed guidelines for further discussion.

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Structure/function relationships relevant to the V3 loop of HIV-1 gp120

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The V3 loop of gp120 strongly contributes to the determination for co-receptor usage. This was established by the '11/25 rule' which states that, if a positive charge is present at the 11th or 25th position in the V3 region, the virus is predicted to be X4-tropic. While this rule is ～90% accurate for R5-tropic viruses, it is< 50% accurate for X4 strains. Moreover, the reason why these positions contribute to co-receptor usage is still unknown. To improve the overall accuracy of predicting virus tropism and to understand the mechanism by which the V3 sequence determines tropism, we used a molecular modeling approach to build 3D models of V3 sequences whose co-receptor usage had been experimentally defined. We found that the amino acids at positions 11, 24 and 25 form a single, contiguous electrostatic surface in the 3D models. This surface presents a positive charge in the X4-tropic viruses and a negative or neutral charge in the R5-tropic viruses. We also analyzed the sequences of the same V3 loops and defined a new rule which has 97% accuracy for predicting co-receptor usage: "*A positively charged amino acid at position 11, 24 or 25 defines X4; otherwise R5*".

We previously reported structural similarities between the central part of the V3 loop and the 40s loop of CC and CXC chemokines (Structure 11 : 225-236, 2003). Thus, we showed that the structure of a V3 peptide bound to a murine anti-V3 monoclonal antibody (mAb) 0.5β that neutralizes a CXCR4-tropic virus resembles the β-hairpin formed by the 40s loop of SDF-1α, and that a V3 peptide bound to human anti-V3 mAb 447-52D that neutralizes many CCR5-tropic viruses resembles the β-hairpins formed by the 40s loops of CC-chemokines MIP-1α, MIP-1β and RANTES. While these findings were based on apparent structural homologies from NMR and crystallographic studies, they might not represent actual native functional similarities. To determine if these structural similarities also reflected similar functions, we constructed several chimeric viruses in which a part of the 40s loop of SDF-1α was substituted for the tip part of V3; we then tested these chimeras to determine their infectivity using a single-round infectivity assay. The most infectious of these chimeras was HX-S1 in which we substituted 7 amino acids of SDF-1α for 9 amino acids at the tip of the V3 loop of HXB2, a virus that uses CXCR4. HX-S1 retained 25-30% of the infectivity of the wild type HXB2. This result demonstrates that the 40s loop of SDF-1α can complement the function of the tip of the V3 loop and suggests that the 40s loop and V3 tip play a common role in targeting CXCR4.

In conclusion, we have elucidated two aspects of the structure/function relationship relevant to the V3 loop: 1) V3 positions 11, 24 and 25 constitute an electrostatic surface on 3D models of V3, and the charge of this "surface patch" contributes to the determination of co-receptor usage; and 2) the structural similarity between the 40s loop and the tip of the V3 loop reflects functional similarities involved in co-receptor usage.