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【特別講演】**特別) HIV-1 Reverse Transcriptase: Mechanisms of Drug Resistance**

Stephen H. Hughes

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Most drugs approved to treat HIV/AIDS inhibit two of the three viral enzymes, protease or reverse transcriptase (RT). One drug inhibits the third enzyme, integrase; two inhibit different aspects of entry/fusion. Unfortunately, HIV can develop resistance to all of the approved drugs. It is important to develop new drugs that are effective against the known drug-resistant mutants. Understanding the mechanism(s) of drug resistance is an important part of this process. There are two classes of approved anti-RT drugs: nucleoside analogs (NRTIs) and nonnucleosides (NNRTIs). NRTIs lack a 3'-OH and act as chain terminators when incorporated into viral DNA by RT. NNRTIs bind in a hydrophobic pocket in RT that is near the polymerase active site. NRTI-resistant RTs have an enhanced ability to discriminate between the analog and a normal nucleoside. There are two basic mechanisms: 1) exclusion, which occurs when the NRTITP is incorporated, and 2) excision, which involves removal of the NRTIMP from the end of the viral DNA. NNRTI resistance usually involves a reduction in the ability of the NNRTI to bind to RT; mechanisms include a loss of hydrophobic contacts, steric hindrance, or a partial block to the entry of the NNRTI.

【教育講演1】

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趣 旨：

A few years after the first reported case of AIDS in the USA, HIV had also established itself in Asia. It spread quickly and by the early 1990s, HIV infections were being reported in every country of Asia. In some, notably Thailand, major epidemics were underway.

A little more than two decades later, an estimated 9 million people in Asia have been infected with HIV, and millions of them have died of AIDS-related illnesses. Even these high numbers cannot convey the suffering and pain experienced by people living with HIV, and their families. Along with the shock of sudden failing health and mysterious illnesses, came public shame and humiliation. Infection did not elicit compassion but condemnation and rejection.

HIV seemed to stoke and focus deep-rooted social prejudices, not least because it was associated with behaviours deemed taboo in ‘polite society’ : drug injecting, sex between men, and commercial sex. Consequently, the initial reactions across Asia tended to be either denial or moral panic.

In most places, the factors driving the epidemics, and the patterns and trends of HIV transmission in Asian societies were poorly researched. This had two effects. In some quarters, it fed the complacent belief that the dominant values in Asian societies would protect them against HIV, and that epidemics would be confined to marginalized groups of people who engaged in taboo behaviours. At the same time, the burgeoning epidemics underway in East and southern Africa sparked fears of similar relentless HIV spread in Asia, and evoked doomsday scenarios in which 10 per cent or more of adults would soon be infected with HIV.

Over the past decade, our understanding of HIV epidemics in Asia has improved to the point where we can safely say that both those prognoses were wrong.

But do we know what HIV holds in store for Asia? What are the driving factors in Asia’s HIV epidemics, and how may these change? What damage are the epidemics wreaking in the countries of this region? How high are prevalence rates likely to become and who will bear their brunt? What are the best strategies for overcoming the epidemics? And are those strategies viable and realistic in Asia today?

Those questions, for the most part, have eluded clear-headed enquiry and satisfactory answers. (From the preface of the report of the Commission on AIDS in Asia “Redefining AIDS in Asia: crafting an effective response”, Oxford University Press, 2008)

EL1) Redefining the HIV epidemic in Asia and crafting an effective response

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As a percentage of the region's large population, HIV prevalence rates in Asia may seem low but the absolute figures are high. According to UNAIDS and WHO estimates, 4.9 million (the range being 3.7 million-6.7 million) people were living with HIV in Asia in 2007, including the 440,000 (210,000-1.0 million) people who became newly infected in that year. Approximately 300,000 (250,000-470,000) people died from AIDS-related illnesses in 2007.

Overall, an estimated 9 million Asians have been infected with HIV since it first appeared in the region more than 20 years ago, and approximately 2.6 million men, 950,000 women, and 330,000 children have died of AIDS-related diseases.

Asian nations like their counterparts in other parts of the world had lost precious time in the early stages of the epidemic first by denying it and later by adhoc responses without a strategic direction. Despite a ten-fold increase in resources and growing political commitment over the last decade, access to essential HIV services for prevention and care in Asia has remained low. Even today, prevention and treatment services fail to reach 2 out of every three people in need of them. Because of this, there are limited successes in Asian national efforts in turning the tide of the epidemic. And as Asian countries continue along this path, AIDS will account for more deaths annually among 15-44 year-old adults than do tuberculosis and other diseases.

The impact of the epidemic is also largely on poor families who have no cushion against the consequences of AIDS-related illness in the near absence of formal social protection schemes. The epidemic is increasingly getting feminised and women are the targets of the worst form of stigma and discrimination. Wives caring for HIV-infected husbands are ostracized, and widows are forced to leave their homes and land.

It was this realization that led to the creation of an independent nine member Commission on AIDS in Asia. The Commission has a good mix of experts from the AIDS field and outside. The Commission reviewed scientific evidence surrounding the spread of HIV in Asia, assessed the medium- and long-term impact of AIDS on Asian societies and recommended practical HIV responses that can have the maximum impact on Asia's HIV epidemics.

The Commission believes that governments in Asia have the information, the institutions and the resources to substantially reduce new infections and to provide access to treatment to all who need it. The unique nature of Asian epidemics, the currently low prevalence, the strength of public and private health systems, and economic prosperity in the region create an opportunity unavailable in many parts of the world. If governments in Asia deploy their financial and human resources prudently, and strengthen partnerships with non-government and community sectors, they will be able to halt and reverse the epidemic within the time-frame set in global declarations on Universal Access and achievement of the Millennium Development Goals (MDGs).

This talk will outline some of the main findings of the Commission and recommend key action points for countries to implement, so that battle against HIV in Asia can be decisively won.

EL2) HIV感染症の治療と予防～過去から未来へ～

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HIV感染症が原因不明の免疫不全症として初めて報告されたのが1981年。以来、不治の病として恐れられていたエイズに、最初の抗HIV薬AZT（ZDV）が入手できるようになるとの情報がいった時（1987年）は、これで何とか治療が出来るようになる、治療が出来るようになれば差別や偏見も少なくなるとの期待が膨らみました。

しかし、現実はその甘くなく、待っていたのは深刻な副作用と、それをやっとな克服したと思ったら、次は単剤の弱みでした。差別と偏見の中から立ち上がったHIV診療の黎明期の、このような苦労と工夫を話して欲しいと小柳会長からお話があり、それが今後の研究や臨床、啓発活動に携わる若い人々にエネルギーを与えることになるのであればと思いお引き受けしました。

AZTの承認から10年の年月を経て1997年から日本でもHAARTが可能となり、世の中は一変しました。HAARTの威力を目の当たりにしたときの感動は忘れることが出来ません。これ程の成果が比較的短期間に得られるようになったのは、科学の勝利と言えます。しかし、これ等の成果は簡単に日本の患者さんに提供できるようになったものではありませんでした。座して待つのではなく、早期導入を目指し常に行政に働きかけ、慣例と言う厚い壁と闘いつつ獲得したものでした。血友病の患者さん達も闘いました。

迅速審査制を採り入れたり、海外のデータで新薬の申請ができるようになったのはHIV感染症/エイズの領域が最初ですし、臨床現場における個人情報保護、インフォームドコンセントの遵守、患者参加型の医療、カウンセラーの配備等を他の医療分野に先駆けて達成させたのもこの分野が最初です。

とは言っても、日本ではまだまだ国民に対する啓発が不十分で、また、世界中の医療機関で行われているPITCに対する医療関係者の認識が欠如しています。まだまだ闘いは継続して行かなければなりません。

EL3) HIV物語・25年史

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1981年に米国に突如出現した後天性免疫不全症候群（エイズ）であるが、そのわずか2年後には原因がTリンパ球に強い親和性を有するヒトレトロウイルスHIV-1（当時は別の名称が用いられていたが）であることがわかった。その後非常に短い期間にHIV感染症は、だれも予測できない規模でパンデミック化した、歴史的な感染症となった。2007年末の世界中のHIV感染者の数は推計約3200万人であり、これまでに既に約6000万人の人が感染したと予想されている。HIV感染者の発症予防については、ある程度のめどが付いているが、ワクチン開発のゴールは今のところ見えない。今年エイズの原因ウイルスHIVがパリではじめて同定されてから25年の節目に当たるので、HIVのユニークな性質とエイズ/HIV制圧の難しさについて、考察を加えてみた。
