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HIV-2 Reverse Transcriptase using Chemical Similarity Process of Reducing Viral Attack and Increasing CD4 Counts in HIV-Infected Patients

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Abstract
The aim of this study is to examine the Chemical processes focused to reduce viral attack and increasing CD4 counts, HIV viral load after initiation of combination antiretroviral treatment. However by purchasing and assaying of selected top-scoring compounds from the library active anti-HIV agents are created. Subsequent synthesis and assaying of S10087 analogs proposed by further computational analysis yielded anti- HIV agents. Thus, with the aid of computational tools, it was possible to evolve a false positive into a true active. Antiretroviral treatment–naive, chronically HIV-infected persons (n = 1376 and n = 1605 for each of the 2 cohorts) are untreated. During the observation period (5 months), at least 1 HIV RNA level and 2 CD4 cell counts may be stable. Approximately 35% were nonwhite, and 45% had risk factors. Currently, the data would generally support initiation of HAART in patients with CD4 cell counts more than 350 cells/µl. However, from the strong potential for confounding in observational studies and the lack of adjustment for lead-time bias in many analyses, it is not possible to rule out possible long-term detrimental effects of earlier use of HAART. In chemical process we can use these chemicals and it is possible to reduce the critical bond in HIV virus and increase the amount of CD 4 counts.

Introduction
HIV/AIDS has caused more than 35 million deaths since 1973, and an estimated 64.2 million people are currently HIV-positive. Despite the availability of the highly active antiretroviral therapy (HAART), 3 million HIV/AIDS-related deaths occurred in 2004. The target for the first three drug classes is HIV-1 reverse transcriptase (HIV-RT), which is vital to replication of the HIV-1 virus by converting its single-stranded RNA into a double- stranded DNA. HIV-RT is a 1000-residue heterodimer consisting of 66-kDa (p66) and 51-kDa (p51) subunits. Participants Antiretroviral treatment–naive, chronically HIV-infected persons (n = 1376 and n = 1605 for each of the 2 cohorts) untreated during the observation period (5 months) and with at least 1 HIV RNA level and 2 CD4 cell counts available. We consider recent data to support the arguments for and against earlier initiation of HAART in patients with CD4 cell counts more than 350 cells/µl. The factors, as yet undefined, likely drive CD4 cell losses in HIV infection. These findings have implications for treatment decisions in HIV infection and for understanding the pathogenesis of progressive immune deficiency.

Background and scope of review
The main effect of HAART is to suppress viral replication, allowing the individual's immune system to recover and protecting him/her from the development of AIDS and death, treatment should be initiated at an early point in the individual's course of disease, prior to a time when CD4 cell loss is such that there is substantial risk of clinical progression. On the basis of evidence that clinical progression rates were low while the CD4 cell count remained above 200 cells/µl but increased rapidly at lower levels, most early treatment guidelines recommended that treatment be delayed until the CD4 cell count had fallen below 200 cells/µl. In addition to their role as predictors of the clinical outcomes of HIV infection, CD4 cell count and plasma HIV RNA level are commonly used as markers of the success of highly active antiretroviral therapy (HAART). To sup- press viral replication so that the VL is below the level of detection with standard assays is thus one of the aims at the start of antiretroviral treatment. HIV-infected patients in most developing countries have limited second and third line antiretroviral treatment options. In many countries in Asia, second-line combination antiretroviral treatment (cART) is not widely accessible.

Methods and Analysis
The data were collected: patient baseline data, CD4 and CD8 count, HIV VL level, prior and new AIDS defining illness (ADI), date and cause of death, prior and current prescribed HAART, and reason for treatment change. CD4 count was calculated by linear regression with the values at time T, before T, and after T, and was expressed as changes of cells per micro liter (µL) per year. The HIV VL was related to the CD4 count slope at time T. Preliminary analyses in eligible TAHOD patients showed that the mean CD4 count slope was significantly higher in the first 6 months after cART initiation than in the period afterwards (179 vs. 44 cells/µL per year, $p < 0.001$). The CD4 slopes were therefore calculated from CD4 counts measured 6 months after cART initiation. We did not include CD4 count and HIV VL at baseline for the following three reasons:

first, a large proportion of patients did not have the tests at treatment initiation (approximately 25% of patients had no CD4 count and 45% HIV VL, Table 1); second, the model aimed to help clinicians in this region to assess the status of immune system with the clinical information at hand (e.g., age, hepatitis status, current CD4 count, time since treatment initiation, etc) where the baseline information on CD4 count and HIV VL may not be readily available; and third, when we included baseline CD4 and HIV VL in a sensitivity analyses based on the subset of patients with baseline data available, the results remained com- parable with the model without the baseline CD4 count and HIV VL. The multivariate models were built using a forward-step approach, the final model included covariates that remained significant at the 0.20 level. Non-significant variables were also presented and adjusted for in the final multivariate models. Finally, sensitivity analysis was also performed by restricting the records in patients contributing at least 4 or more concurrent CD4 and HIV VL tests. The intermolecular structural similarity can be measured through distance and association coefficients. Association coefficients are used with real-value descriptors or binary data, and are often normalized to lie within the range of zero (no similarity at all) and unity (identical sets of descriptors). The crystal structures for HIV-RT complexes with the inhibitor UC-781 (PDB ID: 1rt4) and the K103N variant complexes with the inhibitor TMC-125 (PDB ID: 1sv5). The top ranked compounds obtained in this way were redocked and rescored using the Glide extra-precision (XP) mode. Plasma HIV-2 RNA levels were measured using either the Amplicor HIV-1 Monitor assay or the branched DNA assay, and all values were standardized to their branched DNA equivalents. The CD4 cell counts were measured by flow cytometry using standardized methods; specific instruments varied according to the institution. Descriptive and other basic statistics were computed using Intercooled Stata, version 8.0 (Stata Corp, College Station, Tex). To assess the association between plasma HIV RNA concentration and CD4 cell change, we used random-effects linear models (PROC MIXED, SAS software v.8.2; SAS Institute Inc, Cary, NC) assuming an un- structured correlation structure. We used log10-transformed values of plasma HIV RNA in all analyses. To determine the extent to which inter individual variability in CD4 cell change was explained by presenting HIV RNA measurement, a single value at explaining inter individual variability in CD4 T-cell change, we used a similar approach to generate model-based estimates of HIV RNA change per individual and regressed these estimates on model- derived individual rates of CD4 cell loss. Besides the protein energies, the energy-minimized structures for the complexes provided the intra molecular and salvation energies for the ligands in the protein environment. In the bound state, it was assumed that there is only one conformation accessible to each ligand; its conformational entropy is therefore zero. This approximation should be revisited, though it may require a conformational search in the bound state.

The current evidence for and against earlier initiation of HAART and Modifications of S10087

The main argument for delaying HAART related to the toxicities and inconvenience of these drugs and the fact that treatment was likely to be life-long. It was felt that patients would be unable to maintain the high levels of adherence that are required for successful outcomes. Given the perceived low risk of AIDS and mortality at CD4 cell counts more than 350 cells/µl, it was thought that little would be gained by exposing patients to antiretroviral therapy too soon. There is limited evidence to support an increased frequency of toxicities in those starting HAART with higher CD4 cell counts. The risk of non-Hodgkin's lymphoma was more than twice as high (adjusted hazard ratio of 2.28) in non-HAART users with CD4 cell counts of 200-349 cells/µl compared to those with counts ≥350 cells/µl. The risk of serious non-AIDS diseases was also significantly lower in the immediate arm. Which differ by replacement of the 4-methyl group with 3-fluoro (S10076), 3-chloro, 4-methyl (S10085), and 2, 4-dichloro (S10089). After purification, they were submitted to an anti-HIV assay using infected human T-cells, but they failed to inhibit HIV replication in the MT-2 cells at concentrations up to 100 µM.

Chemical Similarity Search and Process

These four different solutions that minimize the HIV complex bond viral factors simultaneously were obtained, specifically 62% and 54% for the Euclidean and Tanimoto coefficients, respectively. In each solution, the Euclidean and Tanimoto coefficients have identical sets of descriptors, whereas the descriptors for the first are weighted. We used two chemicals for the HIV-I reverse transcriptase process. They are oxalamide linker and tetra methyl piperidine. In oxidation process can use H_2N; but it is a triple bond highly react able chemical. In this chemical progress $(CONH_2)_2$ gets oxidized from hydrogen cyanide to cyanogens. These chemicals cause reaction with body fluids in a fraction of second and also it will block the hydrogen molecules in our body cells. Hence we use is called oxalamide linker and due to which single bond NH and double bond oxide is formed. For the HIV-2 reverse transcriptase process; we are adding P- substituted phenyl ring with these two chemicals.

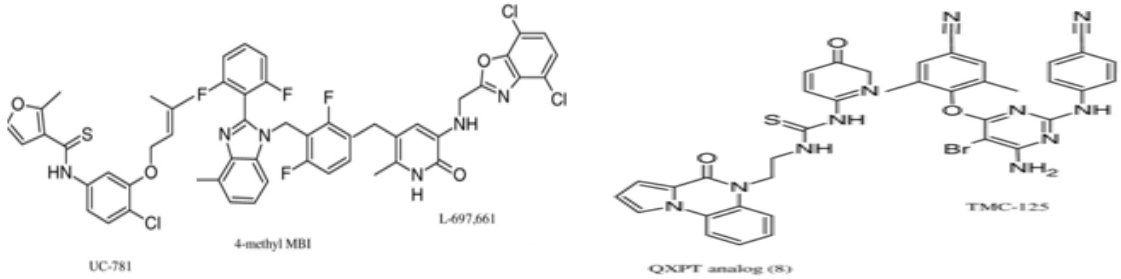

Fig.1. Chemical similarity process in reactive bond higher order chemical reaction

As a link Br is added to P substituted phenyl ring. P denoted Para. It is used for purpose of producing cl. Why we do not go for Meta and ortho is that it produces nitric. Phenyl is a normal chemical. Phenyl ring has a high bond and hence, it cannot be destructed. When HIV virus attacks phenyl ring; chlorine gets produced. The molecules in the chemicals are arranged in the form of chair confirmation. According to genetics and the pattern used for chair confirmation is T257, G473, S375, E370, G429, N425, and W427. These chair confirmation keeps on changing. Phenyl is produced from benzene (C_6H_5). Phenyl groups tend to resist oxidation and reduction. It is used to lower cholesterol in people with hyper cholestrolaemia. Considering normal chemical reaction as base; if weak nudeophile and moderate electrophile are added; no reaction occurs. Considering the previous reaction; weak nudeophile is replaced by bromo benzene and p substituted phenyl ring is added. Similarly moderate electrophile is replaced by oxalamide linker and tetra methyl piperidine. During the chemical similarity process Para isomers substitute bromo benzene phenyl ring reacts with HIV virus and hence chlorination occurs for 55-65%. So this chemical process acts as an antibiotic and it will reduce the critical bonding of HIV chemical bond. After that we will calculate CD4 counts. MW (molecular weight), FOSA (the hydrophobic component of the total solvent accessible surface area (SASA)), FISA (the hydrophilic component of SASA), and HB donor (number of hydrogen bonds donated by the solute to water molecules), appear in all solutions. The amino group in 23p and 23o is responsible for the larger de salvation and intra molecular penalties, but provides a more favorable electrostatic interaction with the enzyme due to hydrogen bonding with the Glu138 carboxyl ate group. The pyrimidine and the diarylamino nitrogens are now hydrogen bonded to the backbone nitrogen and oxygen atoms of Lys102, while the amino group of TMC-125 is no longer hydrogen bonded to Glu138. In spite of that, the activity of TMC-125 is not significantly affected by the K103N mutation.

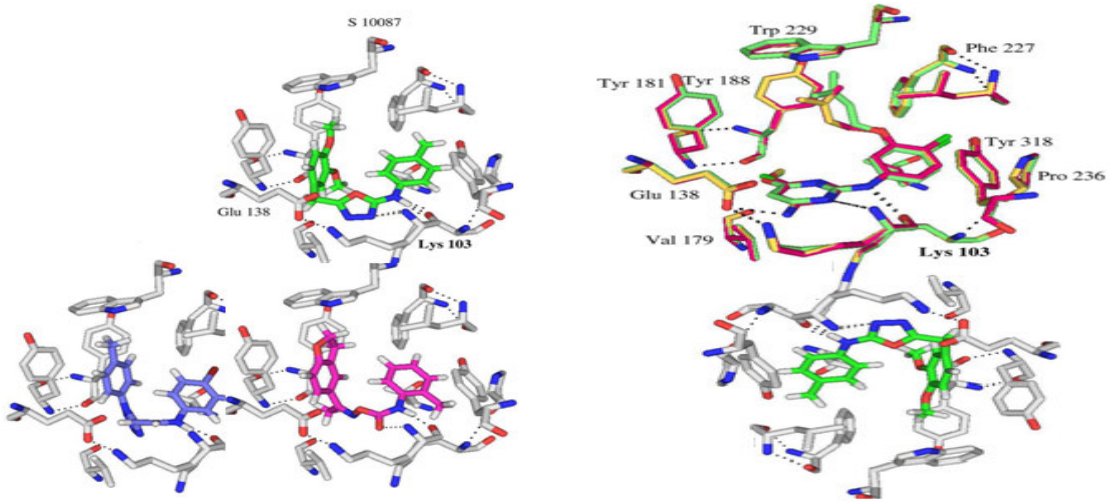

Fig.2. Energy-minimized complexes structure for chemical similarity process.

Process of CD4 counts and treatment response of different CD4 levels

In particular, reported that only 20, 26, and 46% of those starting HAART with CD4 cell counts of less than 50, 50-200, and 200-350 cells/µl reached a CD4 cell count more than 800 cells/µl after 7 years of uninterrupted HAART compared to 73 and 87% of those starting HAART with CD4 cell counts of 350-500 and ≥500 cells/µl. It is important to consider that there may be a CD4 cell count 'ceiling' above which an individual's CD4 cell count is unlikely to rise - this may result in an inverse association between the pre-HAART CD4 cell count and CD4 increases. Thus, immune activation may be a major determinant of T-cell turn- over and CD4 cell depletion in chronic HIV infection both in human and animal hosts. Our results provide further support for additional studies exploring the relative contribution of immune activation to the pathogenesis of immune deterioration in treatment- naive, HIV-infected persons. Recently, investigators from the North American AIDS Cohort

Collaboration on Research and Design (NA-ACCORD) group reported that initiation of HAART at a CD4 cell count between 350 and 500 cells/µl was associated with a 70% improvement in survival compared to starting HAART at lower CD4 cell counts; the authors also used methods to take account of lead-time bias. The below slope was associated with age (-5.7 cells/µL per year per 10-year age increase, p = 0.013), concurrent HIV VL (-42.1 per 1 log10 copies/mL VL increase, p < 0.001), concurrent CD4 count (+1.9 per 100 cells/µL increase), disease stage (compared to CDC category A illnesses: +29.2 if diagnosed with tuberculosis [TB] with or without other ADI, p < 0.001; +15.7 if diagnosed with non-TB ADI, p = 0.011), hepatitis B or C co-infection (-21.3 if co- infected, p = 0.007), and time since cART initiation (compared to CD4 slope during 6-12 months: -23.8 during 12-18 months, p = 0.130; -39.5 during 18-24 months, p = 0.005; -64.8 at 24 months or later, p < 0.001). The CD4 counts continues to increase with HIV VL up to 5 000 copies/mL during 12-18 months after cART. If this patient was hepatitis co-infected, the CD4 count starts to fall when the HIV VL increases up to 3 000 copies/mL .

Table.1. Analyses of CD4 count (slope, cells/µL per year)

		Univariate			Multivariate** (95% CI)		
		Difference*	(95% CI)	p value	Difference*		p value
Sex							
	Male*	**0.0**			**0.0**		
	Female	**8.6**	**(0.1, 16.7)**	**0.039**	**8.9**	**(-1.7, 15.1)**	**0.097**
Current age							
	per 10 years older	**-7.3**	**(-16.2, -3.1)**	**0.001**	**-5.7**	**(-14.4, -2.0)**	**0.013**
Disease stage							
	CDC Category A*	**0.0**			**0.0**		
TB with or	**without other ADI**	**27.5**	**(17.2, 38.3)**	**< 0.001**	**29.2**	**(15.6, 39.9)**	**< 0.001**
	Non-TB ADI(s)	**5.3**	**(-7.2, 15.3)**	**0.423**	**15.7**	**(3.5, 23.2)**	**0.011**
Hemoglobin level							
per 1 g/dL higher		**0.0**	**(-0.0, 0.1)**	**0.661**	**0.0**	**(-0.0, 0.1)**	**0.689**
Concurrent CD4 count							
Per 100 cells/µL higher		**2.1**	**(-0.4, 4.0)**	**0.321**	**2.9**	**(0.2, 4.7)**	**0.224**
Concurrent viral load							
per log10 copies/mL higher		**-42.3**	**(-51.8, -37.5)**	**< 0.001**	**-42.1**	**(-51.3, -36.7)**	**< 0.001**
Hepatitis B or C co infection							
No*		**0**			**0**		
Yes		**-23.7**	**(-37.3, -7.6)**	**0.005**	**-21.3**	**(-34.9, -5.1)**	**0.007**
Time since cART initiation							
> 6 to ≤ 12 months*		**0.0**			**0.0**		
> 12 to ≤ 18 months		**-23.6**	**(-39.7, -5.3)**	**0.131**	**-23.8**	**(-39.8, -5.5)**	**0.130**
> 18 to ≤ 24 months		**-37.1**	**(-43.1, -7.4)**	**0.007**	**-39.5**	**(-46.2, -9.5)**	**0.005**
> 24 or more months		**-63.7**	**(-82.4, -53.1)**	**< 0.001**	**-64.8**	**(-83.5, -54.2)**	**< 0.001**
Initial cART containing NNRTI							
No*		**0.0**			**0.0**		
Yes		**7.1**	**(-1.4, 17.3)**	**0.235**	**-2.5**	**(-9.2, 8.9)**	**0.874**
Initial cART containing boosted PI							
No*		**0.0**			**0.0**		
Yes		**-1.1**	**(-13.7, 6.0)**	**0.893**	**-4.5**	**(-16.1, 3.3)**	**0.440**
Initial cART containing abacavir							
No*		**0.0**					
Yes		**-13.7**	**(-26.3, 0.0)**	**0.078**	**-7.6**	**(-19.7, 7.3)**	**0.072**

Results and discussion

1378 to 1605 naïve patients initiated cART, and had three or more concurrent CD4 and HIV VL data pairs available beyond 6 months after cART initiation. After cART initiation, viral logical suppression (HIV VL < 400 copies/ mL) was achieved in 83% of patients at 6 month and 82% in 12 months. Table shows the random-effect linear regression analysis of the CD4 count slope. Concurrent hemoglobin level, initial cART containing NNRTI or boosted PI were not significantly associated with the study endpoint in both Univariate and multivariate analyses. Recommendations for earlier treatment are therefore unlikely to have any major effect on population-level outcomes, and it is argued that the resources required for earlier treatment may be better used to encourage earlier HIV testing in these countries, or enabling full access to HAART in countries where drugs are less readily available. Jerwin prabu et al observed in HIV-infected patients with HBV or HCV an initially delayed CD4 count recovery at week four after HAART treatment, but at week 48 the CD4 count increase was similar to the patients only infected with HIV . A decrease in CD4 count slope of less than 20 cells might not be clinically significant in the early phase of cART. Phenyl groups tend to resist oxidation and reduction. It is used to lower cholesterol in people with hyper cholestrolaemia. Considering normal chemical reaction as base; if

weak nudeophile and moderate electrophile are added; no reaction occurs. Considering the previous reaction; weak nudeophile is replaced by bromo benzene and p substituted phenyl ring is added. Similarly moderate electrophile is replaced by oxalamide linker and tetra methyl piperidine. During the chemical similarity process Para isomers substitute bromo benzene phenyl ring reacts with HIV virus.

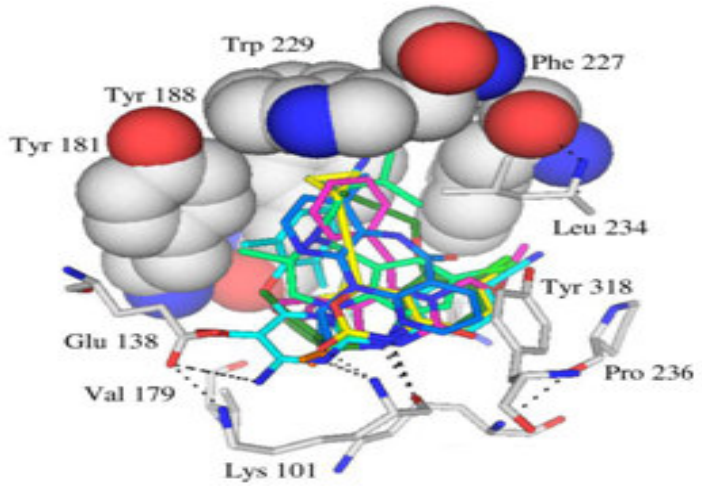

Fig.3. Molecular reaction with strong chair confirmation

If CD4 count is the only way for monitoring treatment response, the result of this analysis showed that a patient can have a considerable duration of virological failure without meeting CD4 criteria recommended by WHO for switch of ART to second line, through the possible development of HIV- drug resistance that could compromise the efficacy of later cART regimens remains uncertain.

Conclusion

Subsequent synthesis and assaying revealed that S10087 was in fact a “near-miss” since several closely related analogs were found to be potent anti-HIV agents. A chemical similarity of the HIV-2 reverse transcriptase as reference structures in order to identify potentially active compounds. The results of our study challenge the concept that CD4 cell depletion in chronic HIV infection is mostly attributable to the direct effects of HIV replication. Thus, with the aid of computational tools, it was possible to evolve a false positive from the virtual screening into a true active. In this research we have summarized the evidence for and against earlier initiation of HAART in HIV- infected individuals with a CD4 cell count more than 350 cells/µl. The effect on long-term outcomes through the possible development of HIV drug resistance remains uncertain.

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