Study on NNRTIs Treatment for HIV-1 by Comparison of RPV and EFV

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Keywords: AIDS, Treatment, RPV and EEV.

Abstract: AIDS （acquired immune deficiency）is a disease caused by progressive failure of immune system, allowing cancer and opportunistic infection to survive. Without any therapy being taken, people who get HIV/AIDS could only survive 9-11 years. AIDS are not only difficult to detect, Aids also spreads easily through several ways. It could spread through the contact of blood, pre-ejaculate, semen, vaginal fluid and other body humor. A simple contact with patient's humor could cause the infection to happen. From the first-time researchers discovered AIDS IN 1981, there are more than 32 million people died because of AIDS. The severity of the disease could be seen in these large infection numbers. Until now, researchers had not found any useful method to cure the disease. What researchers could do is only to try to make the patient live longer. This essay is aimed on the comparison of two drugs (Rilpivirine and Efavirenz) which could help the Aids patient to live longer and find out why the second generation rilpivirine (RPV) will be better than the first generation Efavirenz (EFV). CCS concept: Professional topics, Life and medical sciences, Architectures.

1 INTRODUCTION

The first sample of AIDS was discovered by CDC in 1981 and published on the Morbidity and Mortality weekly report. Then, after having some research, this disease soon been named as AIDS. After then, AIDS soon spread to every continent in the world and become one of the most difficult disease to be cured.

The reason makes the disease spread so fast is because Aids could spread easily by the contact of humor of human body, including blood, semen and vaginal fluid. It normally spread through sexually and condomless contact with AIDS patient. On the other way, a mother who have AIDS could also bring the disease through pregnancy and the process during the birth. These two particular ways to spread help us to limit the ages people who are easily get AIDS, which is 18-45. This is because normally people at this age would have most of sex life in their whole life time and most of mother will be pregnancy in this period.

The large year period which people could easily get AIDS makes the disease spread quickly in the world. By the spreading of disease, it causes huge effects on society and makes people realize the severity of the disease. In 2018, 37.9 million people were living with HIV and it resulted in 770,000 deaths. Between the time that AIDS was identified (in the early 1980s) and 2018, the

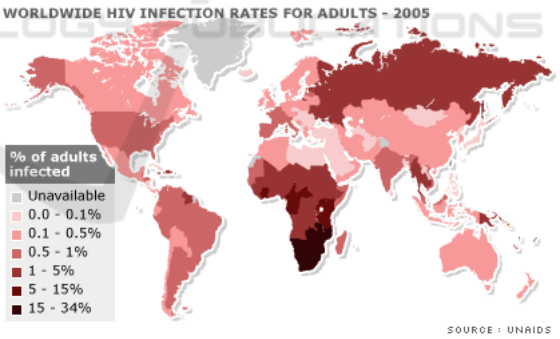

Figure 1. The global percentage of infecting HIV.

disease caused an estimated 32 million deaths worldwide. As the graph shown here, most of the countries have an infected rate more than 0.1%-0.5%, even there is country has a rate of 15%-34%. The graph could certainly prove that the speed it spread and the large numbers of infections.

Large base numbers of patients show similar symptoms after getting infected. Most of the patient firstly get Flu in the early stage of AIDS and at the later stage those patients will get fever, large lymph nodes and weight loss.

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AIDS has had a large impact on society, both as an illness and as a source of discrimination. The disease also has large economic impacts. This is because particularly in China and some other country who may still have a conservatism concepts to sexual life will show extreme discrimination and stereotypes to the people who get AIDS and considered them as dissipated people. However, those people who get AIDS could be infected by unconsciously contact with the infected people. These stereotypes cause large difficulties to the infected people in the society. On the economically part, it also creates large burdens for the patients to buy the particular drugs and take the treatments. Because there are no drugs could completely cure the AIDS, so the treatment will last a long period, leading to a severe economic burden to the family or individual.

2 TREATMENT

Currently, the most effective way to inhibit the AIDS is to use antiviral treatment. These antiviral treatments include NNRTIs (non-nucleoside reverse transcriptase inhibitor). However, the first time we discover NNRTIs and other drugs which could be used as a treatment could be retrospect to decades before, including the two drugs, RPV and EFV. In the summer of 1981, the acquired immunodeficiency syndrome was first discovered by people. Two years later the etiological link to AIDS, the human immunodeficiency virus (HIV) was identified. Since the identification of HIV, the development of effective antiretroviral drugs and the scientific achievements in HIV research has been vital. The first NNRTI(nevirapine) was discovered by researchers at Boehringer Ingelheim . In 1996, it was approved by FDA. In the next two years two other NNRTIs were approved by the FDA, delavirdine and EFV in 1997 and 1998 respectively. These three drugs are the first generation NNRTIs treatment. The yearning to get for NNRTIs with better resistance profile led to the development of the next generation of NNRTIs. Janssens Foundation and Tibotec's researchers discovered the first drug in this class, etravirine. It was approved in 2008 by FDA. The second drug in this class, RPV, was also discovered by Tibotec and was approved by the FDA in 2011.

2.1 Nomenclature

rilpivirine: 4-{[4-({4-[(*E*)-2-cyanovinyl]-2,6-dimethylphenyl} amino) pyrimidin-2-yl] amino} benzonitrile

Efavirenz: (4*S*)-6-Chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-2,4-dihydro-1*H*-3,1-benzoxazin-2-one

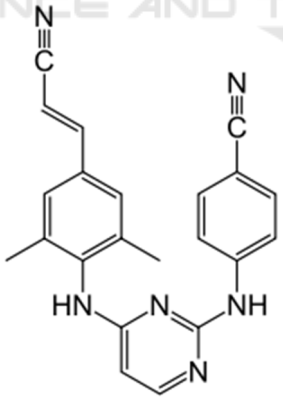

Figure 2. The structure of Rilpivirine

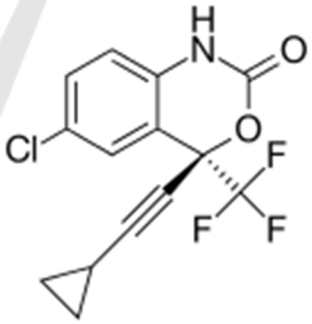

Figure.3 The structure of Efavirenz

2.2 Chemical Properties

Table 1 the basic properties of RPV and EFV.

	Molar mass	formula	Half life
RPV	366.428 g·mol^{-1}	$C_{22}H_{18}N_6$	38 hours
EFV	315.68 g·mol^{-1}	$C_{14}H_9ClF_3NO_2$	40–55 hours

3 THE PHARMACOLOGY

3.1 Introduction of RT: The Targets of NNRTIs

RT is one of the most important enzymes for HIV to spread in the host cell. During uncoating, the single-stranded RNA genomes within the core or capsid of the virus are released into the cytoplasm. HIV now uses the enzyme reverse transcriptase to replicate the RNA genome. Normal transcription in nature is when the DNA genome is transcribed into mRNA which is then translated into protein. In HIV reverse transcription, RNA is reverse-transcribed into DNA.

3.2 The Targets of NNRTIs and the Function Affected by NNRTIs

NNRTIs could inhibit the polymerization of HIV RT, which is an essential viral enzyme in the process to produce double-stranded viral DNA genomes from the single strand viral DNA genome. RT is a heterodimer of p66 and p51. P66 is formed like people's right hand. It contains the thumb, fingers, palm and connections subdomains. Although the exact mechanisms of NNRTI action is not clear yet, it is commonly agreed that the using of NNRTIs to the drug-binding pocket of HIV-1 RT would lead to a reposition of the template-primer, therefore guarding against the dNTP binding to form a competent RT-DNA-dNTP complex. Moreover, non-competitive NNRTIs allosterically target a hydrophobic pocket. What needs to notice is that NNRTIs is only useful to the HIV type 1 but not HIV type 2. This is because HIV-2 RT possesses isoleucine at codon181 and leucine at 188. Both of the amino acids there could prevent the NNRTIs binding to the pocket. (Figure. 4).

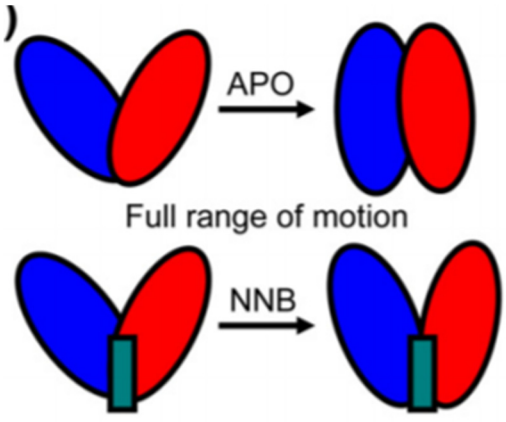

Figure. 4: The binding process.

E.g. This is a graph showing the comparison between the original hinge motion and the hinge motion after using the NNRTIs (Ivetac, McCammon 2009). The thumb is colored in blue and the fingers is colored in red. The hinge motion is the process that thumb and fingers close and become a straight line. However, as the graph has shown, the NNRTIs acts like a wedge in the center of the thumb and fingers. This "wedge effect" prevent the full closure of the hinge motion. Then, the NNRTIs inhibits the RT to replicate one single strand of DNA into double helix structures.

3.3 Mode of Delivery

Depending on the different function of different medicines and the different doses, each particular medicine requires a different way to deliver them.

3.3.1 The Mode of Delivery of RPV

Traditionally, RPV is delivered orally by patients with 25mg once-daily(Williams, Crauwels, Basstanie 2015, Sanford 2012). Rilpivirine should always be taken with a meal to make sure that there is adequate exposure. However, there are several recent studies which are researching the effects of RPV-LA (Long acting RPV). This type of RPV is focusing on the different mode of delivery of RPV. Currently, the RPV-LA pharmacokinetic data showed that therapeutic concentrations of RPV can be maintained for at least 28 days after intramuscular administration of doses between 600 and 1200 mg (Ferretti, Boffito 2018), with high RPV levels achieved in rectal tissue and in vulvovaginal secretions. With regards to HIV prevention, a study in HIV negative women showed that RPV-LA is generally safe and well tolerated and accepted in this group (Cohen, Molina, Cahn, Clotet, Fourie, Grinsztejn, Boven 2012). What makes the new type of the mode of delivery attracting is that it could overcome the adherence issues and relieve the pill burden of patients. It is more patient-friendly than orally available RPV tablets.

3.3.2 The Mode of Delivery of EFV

EFV is delivered orally by the patient once-daily. The recommended dosage once-daily should be 600mg (Ivetac, McCammon 2009), taken on an empty stomach, and favorable at bedtime, to diminish possible neuropsychiatric side effects. Efavirenz is contraindicated in pregnancy (category D) because it can cause fetal harm in the first three months.

However, a recent study conducted by Kamboj, S., Sethi, S., & Rana, V. in 2018 gives a new idea in

the mode of delivery in order to raise the bioavailability of the EFV. The new deliver mode was described as EFV1. It turns to a lipid base delivered mode (Kamboj, Sethi, Rana 2018, Varshosaz, Taymouri, Jahanian-Najafabadi, Alizadeh 2018)). This particular mode focused on QbD-driven systematic development of EFV loaded isotropic mixture (IM). It contains long chain triglycerides that have an ability to abolish unstable absorption and obliterating the food associated variabilities which could possibly enhances oral bioavailability.

3.3.3 Comparison of Different Modes of Delivery

With all the existed data and clinical trials have shown, the orally available RPV has a high bioavailability than the orally available EFV for the problems of different structures of the medicines. However, researchers find that RPV-LA does not significantly enhance the bioavailability of the RPV, while the EFV1 (isotropic mixture) shows that it could overcome the food associated effects and the erratic absorption of the drug. EFV seems to have a great potential on overcoming the existed problems and becoming more bioavailable for patients.

3.4 Result

3.4.1 Pharmacokinetics of EFV

Efavirenz, a benzoxazinone compound, has 40%-45% (Figure 2) oral bioavailability. After a single dose of EFV orally administered to volunteers who are not infected, its maximum plasma concentration (Cmax) is 4.1 μg/mL by 5 hours. Efavirenz is suitable for a once-daily regimen because the plasma half-life (t1/2) of single-dose EFV (52 to 76 hours) is similar to that of multiple-dose EFV (40 to 55 hours) (Adkins, Noble, 1998) 90% of efavirenz is metabolized in the liver by the cytochrome P450 3A4 and 2B6. About 14 to 34% of a radiolabeled dose of efavirenz 400mg was excreted in the urine in the form of metabolites and 16 to 61% was excreted in the faeces as unchanged drug. Less than 1% of an administered dose of efavirenz is excreted unchanged in the urine.

Table 2: The properties and experimental data of different kinds of NNRTIS.

NNRTIs	Absorption#			Elimination		Distribution		Metabolism		Ref.
	F	C_{max} (μg/mL)	T_{max} (h)	$t_{1/2}$ (h)	CL (L/h)	Vd (L/kg)	PPB	Major CYP	Effects on CYP	
Nevirapine	>90%	2	4	45	1.5	1.21	60%	3A4,2B6	Induction	*
Delavirdine	85%	7.22[&]	1.17	2.39	60.3	0.8-1	98%	3A4,2D6	Induction	[26]
Efavirenz	40-45%	4.1	5	52-76	9.4	3.8	99.5%	3A4,2B6	Induction	[29,30]
Etravirine	NA	0.40	4	30-40	43.7	6	99.9%	3A4,2C9,2C19	Induction or inhibition	[40,121]
Rilpivirine	NA	0.15	4	34-55	11.8	NA	99.7%	3A4,3A5	NA	[53]
Doravirine	64%	0.96	1.5	12-21	3.73	60.5L	76%	3A4	No effect	[67,68]

This is a snap shot taken from Current and emerging non-nucleoside reverse transcriptase inhibitors (NNRTIs) for HIV-1 treatment. (Wang, Y., De Clercq, E., & Li, G. (2019). Current and emerging non-nucleoside reverse transcriptase inhibitors (NNRTIs) for HIV-1 treatment. Expert Opinion on Drug Metabolism & Toxicology.)

3.4.2 The Pharmacokinetics of RPV

RPV is a diarylpyrimidine compound with a high oral bioavailability. After the oral administration, the maximum plasma concentration (Cmax) of RPV is generally achieved within 4 hours (Tmax). RPV has a long half-life (t1/2=34-55h)(Wang, Clercq, Li, 2019; Garvey, Winston, 2009), which is suitable for its once-daily dosing. Since RPV is primarily metabolized by CYP 3A4 and 3A5, administration with other drugs that induce or inhibit CYP3A could be influential to the concentration of RPV. RPV can effectively inhibit HIV-1 wild-type strains (EC50: 0.51 nM). Moreover, the EC50(half maximal effective concentration) values of RPV are generally lower than that of NVP, EFV, and ETR in the inhibition of HIV-1 group M isolates.

3.4.3 Comparison of RPV and EFV on the Efficacy, Safety and Tolerability

Seemingly, EFV has a longer half life than RPV. It means that the time of EFV to be metabolize half is longer than RPV. However, the terminal half life of RPV is 55h and it shows non-inferior efficacy than EFV. For comparison of oral bioavailability of EFV and RPV, it is only described as high oral availability but does not give exact values. What the data presents is only the bioavailability of EFV which is 40-45%. It is not an effective number. Therefore, by researching on a designed trial to test the efficacy, safety and tolerability, it tells that 346 patients were randomly assigned to take RPV and 344 to take EFV and take at least one dose of study drug. The virological failures of RPV was 13% versus 6% of EFV (11%vs 4% respectively by ITT-TLOVR). Rash, dizziness, and nightmares, even thoughts to suicide were more commonly appeared with EFV (Jackson, McGowan 2015). (This experiment is carried by Jean-Michel Molina, Pedro Cahn, Beatriz Grinsztejn, Adriano Lazzarin, Anthony Mills, Michael Saag, Khuanchai Supparatpinyo, Sharon Walmsley, Herta Crauwels, Laurence T Rimsky, Simon Vanveggel, Katia Boven, ECHO study group). According to the results given in the experiment, it shows that although RPV has a higher rate of virological failure, it is safer and has a higher tolerability than EFV. No doubt the virological failure could affects the therapy taken by patients, but the safety issues and the side effects should definitely be more vital than the progression of the therapy.

3.5 Conclusion

For comparison, there are several differences could help researchers to decide why the second generatioN RPV is better than the first generation EFV. On the side of the mode of delivery, RPV seems to be more convenient. It does not need extra time to take the pills and to notice when people have empty stomach. To determine if people have an empty stomach will be much difficult to determine whether people have food in their stomach. Therefore, on the mode of delivery, RPV is more convenient than EFV. On the pharmacokinetics side, RPV has a similar bioavailability as EFV does. However, considering the safety issue, EFV has more side effects than RPV. RPV is much safer than EFV. With the similar efficacy, RPV will definitely becomes the more popular one. Therefore, RPV could be the second generation of HIV treatment of NNRTIs.

4 CHEMICAL SYNTHESIS

4.1 Chemical Synthesis of the RPV

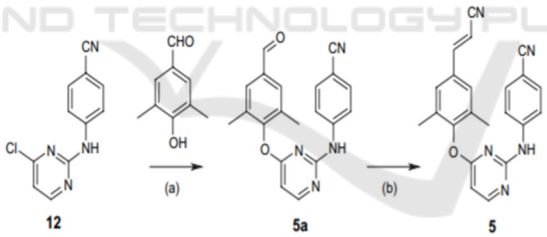

Figure.5: The chemical synthesis method of RPV(Mordant, Schmitt, Pasquier, Demestre, Queguiner, Masungi, Guillemont 2007).

Compound 5(RPV) was synthesized in two procedures from derivative 12. After heating (150 C) the chloropyrimidine 12 and researchers use 3,5-dimethyl-4-hydroxybenzaldehyde with sodium hydride in a 1:1 ratio mixture of NMP dioxane to displace the chlorine on the pyrimidine (Namasivayam, Vanangamudi, Kramer, Kurup, Zhan, Liu, Byrareddy 2018, Mordant, Schmitt, Pasquier, Demestre, Queguiner, Masungi, Guillemont 2007). A Wittig reaction on 5a then happened to form the RPV. A Wittig reaction usually happened on the aldehyde. There is an aldehyde on 5a and with same charge, it could be replaced with a carbon connected to the cyanide. Then, RPV is synthesized.

4.2 Chemical Synthesis of EFV

The synthesis of EFV starts with 4-chloroaniline (43). In order to introduce the trifluoroacetyl group into the chlorine, the amino group is protected as tert-butyl carbamate, followed by reaction with n-butyllithium/ethyl trifluoroacetate. The tert-butyl carbamate was deprotected with HClCH3COOH in 45 to obtain 46, which was crystallized and purified at 5°C and separated with a yield of 87%. For further

reactions, 46 forms need to be neutralized. Therefore, it can be stirred with NaOAc in MTBE to get 47. The p-methoxybenzylation reaction is carried out by p-methoxybenzyl alcohol, which is a cheap and less toxic alternative previously reported for 103, forming 48 (90% yield). Enantioselective alkynylation of compound 48 with 49 enantiomer 48 in the THF-toluene-hexane mixture at -50°C in the presence of ligand 50, the yield was 51%, The body excess (ee) is 98.5%. Cyclization of 51 by COCl 2 /TEA with a yield of 95%, and then deprotection of p-methoxybenzyl by cerium ammonium nitrate to obtain EFV (53) with a yield of 76%. However, p-methoxybenzyl deprotection and cerium ammonium nitrate are by-products such as p-methoxybenzaldehyde and some cerium salts. Therefore, another method was studied, in which 51 reacted with DDQ in toluene to obtain 54a/54b, and then reacted with NaOH-MeOH to obtain amino alcohol 55 (yield 94%). The by-product p-methoxybenzaldehyde was It is converted into p-methoxybenzyl alcohol by reduction with NaBH4. Phosgene can achieve a ring closure of 55 and obtain EFV (53) with a yield of 95% (purity> 99.5%, enantiomeric excess or ee greater than 99.5% after ee-heptane crystallisation), and try to convert it by methyl carbamate After 55-ring closed recrystallization, only EFV was obtained with a yield of 83%. Using p-nitrophenyl carbamate, the yield reached 94%.

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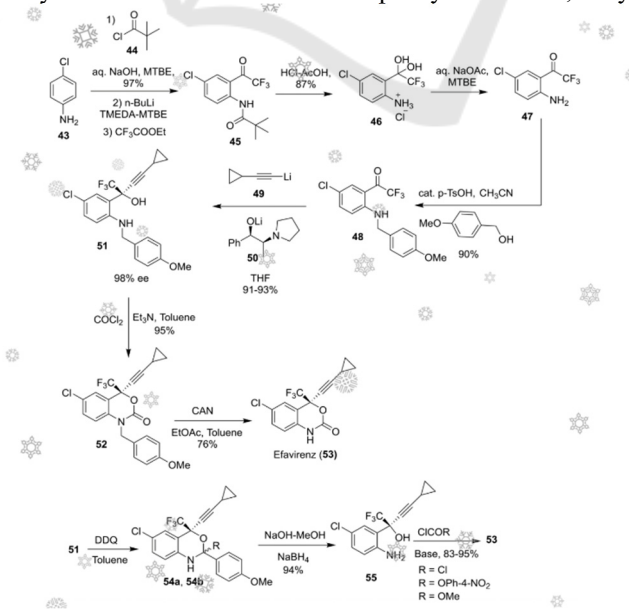

Figure.6 The synthesis method of EFV (Namasivayam, Vanangamudi, Kramer, Kurup, Zhan, Liu, Byrareddy 2018)

Resource delivered from:
RPV
Invented RPV

The main building blocks 77 and 83 (Scheme 13) are the main parts in the reaction.

117, 146-149 is the basic compound synthesis requirements of RPV. 77 is prepared from thiouracil (74), which can be purchased in bulk. Thiouracil (74) used MeI/NaOH to form75% yield at 60°C with a yield of 90%, then react with 68 at 150°C to obtain 76 with a yield of 70%. Then by using POCl3 to carry out the halogenation reaction of 76 to obtain 80% yield of 77

117,146−149 Compound 83 (another key intermediate) is prepared from 3,5-4-bromo-2,6-dimethylaniline in four steps

(78). Use N,N-dimethylformamide dimethylacetal to protect the amino group in 78 to form dimethyl (79). It forms 80, then react with n-butyl lithium to Give 81. Compound 81 carries the Wadsworth-Emmons Reaction. Protection of dimethylformamide with (diethoxyphosphino)acetonitrile followed by ZnCl2 gave the 83 compound. 77 and 83 are reacted together at 150°C to obtain RPV

5 DRUG ECONOMICS

5.1 Cost of RPV and EFV

According to the research to different pharmacies, the research shows that no matter how great the discount the pharmacies are giving, all of the RPV is more than 1000 dollars for 30 tablets per month. Comparatively, EFV has a price among $981–1,177, which is slightly cheaper than RPV.

5.2 Potential

Edurant (Brand name of RPV), received a thumbs up back in 2011 and has achieved annual sales growth ever since. In 2017, the drug raked in $714 million, an increase of 25% from the year prior. However, according to the resources available, the Atripla (efavirenz, emtricitabine, and tenofovir) has a sale of $3.470 billion in 2014. Atripla has a higher sale than RPV. However, RPV has a greater sale increasing speed than atripla. Atripla even have lower sales in 2014 than 2013. In the long term, RPV has more potential than Atripla.

6 CONCLUSIONS

By collecting the data of RPV and EFV, we compared and analyzed the two drugs from three dimensions: pharmacology, chemical composition and price. Based on the comparison of actual data, we finally come to the conclusion that EFV is better in application. I hope our work can play a reference role in the medical application of life-prolonging drugs for AIDS patients.

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