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Treatment of HIV/AIDS with "Dolutegravir-Based Regimen" Antiretroviral Therapy

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Abstract:

Current guidelines recommend dolutegravir (DTG) as the first-line antiretroviral regimen in the treatment of HIV/AIDS. DTG is a second-generation integrase strand transfer inhibitor that has demonstrated high potency, high genetic barrier to resistance, tolerability, minimal drug-drug interactions, and convenience. DTG is also used in a 2-drug regimen among treatment-naive individuals, as well as for switching regimens in virally suppressed HIV/AIDS patients with impaired renal function. However, DTG also has a few considerations. Firstly, DTG has revealed drug-drug interactions with antacids containing aluminum or magnesium, as well as with food or medications containing calcium, iron, or multivitamins, and metformin. Secondly, DTG can increase serum creatinine levels without impacting glomerular filtration rate by inhibiting tubular creatinine secretion. Finally, there was previously a recommendation against using DTG in pregnant women due to concerns about an increased risk of neural tube defects. However, it has been found that the incidence does not differ significantly from the general population. Therefore, almost all current guidelines permit the use of DTG in reproductive-age women and during pregnancy.

Keywords: Dolutegravir, Integrase strand transfer inhibitor, HIV/AIDS

The first report of AIDS patients occurred in 1981 among men who have sex with men (MSM) with *Pneumocystis Carinii* Pneumonia (PCP) in San Francisco and major cities in the United States and Western Europe. The cause of these patients having compromised immunity and being susceptible to opportunistic diseases was initially unknown. It wasn't until 1984 that it was discovered that the low immunity was due to an RNA virus that entered the human body through sexual contact or exposure to infected blood or secretions. This virus destroyed T helper cells, reducing their count from the normal average of 700 cells/mm^3 to below 200 cells/mm^3, which is considered full-blown AIDS. The CD4 T cell count continues to decline until it reaches zero, leaving the immune system weakened and susceptible to various opportunistic infections, ultimately leading to death. Treatment of infected individuals with antiretroviral

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drugs can suppress the virus in the plasma to undetectable levels, resulting in increased immunity and a return to normal quality of life among people living with HIV/AIDS (PLWHA).[1,2]

The evolution of research in developing antiretroviral drugs for HIV has been continuous and accelerated to improve the quality of life for PLWHA. The important classes of antiretroviral drugs are as follows.[3]

1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs): The first drug in this class was Zidovudine (ZVD or AZT), discovered in 1987, followed by Zalcitabine (ddC), Didanosine (ddI), Lamivudine (3TC), Abacavir (ABC), Tenofovir disoproxil fumarate (TDF), and Tenofovir alafenamide (TAF).

2. Protease Inhibitors (PIs): These drugs are used in combination with NRTIs in a regimen known as Highly Active Antiretroviral Therapy (HAART), which began in 1995. HAART can change the course of AIDS from being fatal to having high immunity similar to that of healthy individuals, improving the quality of life. Including Atazanavir (ATV), Ritonavir (RTV), Lopinavir/ritonavir, and Darunavir (DRV).

3. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): These include Nevirapine (NVP), Efavirenz (EFV), and Rilpivirine (RPV), which have similar efficacy to Protease Inhibitors.

4. Integrase Strand Transfer Inhibitors (INSTIs): This class includes Raltegravir (RAL), Dolutegravir (DTG), Elvitegravir (EVG), and Bictegravir (BIC).

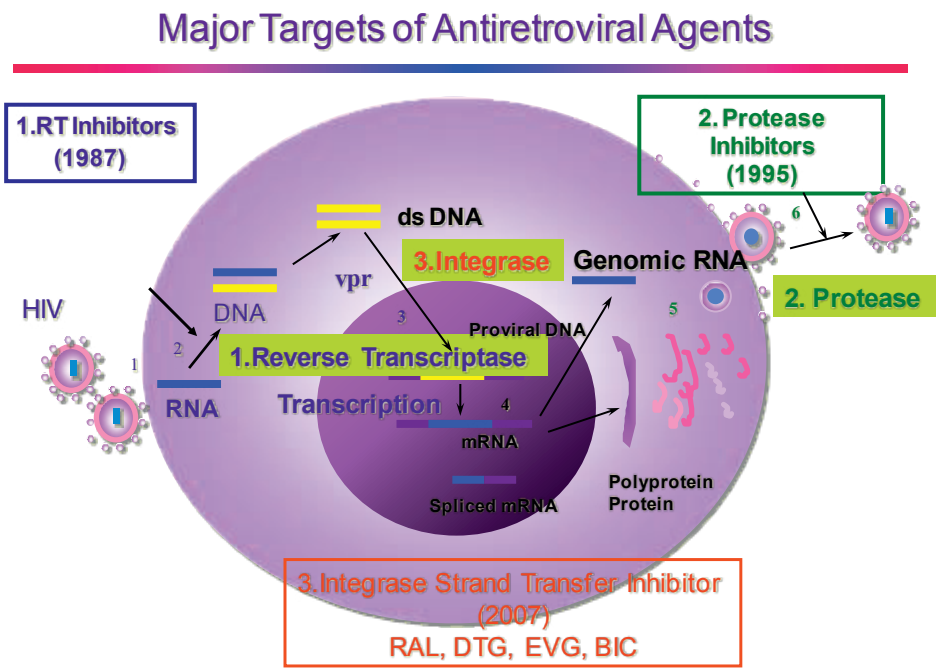

Figure 1 Major Classes of Antiretroviral Therapy

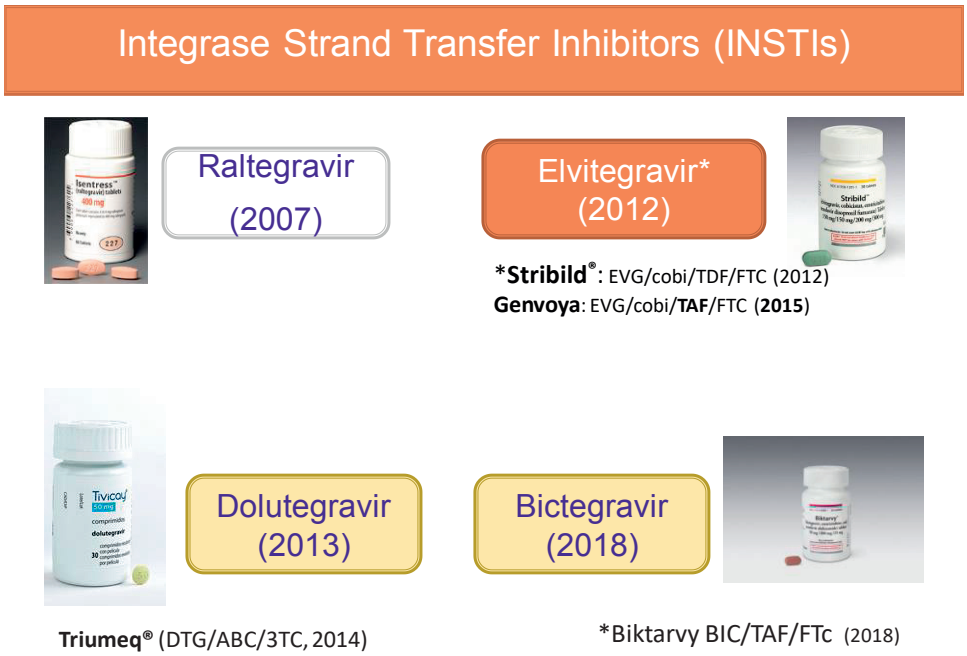

Figure 2 Types of Integrase Strand Transfer Inhibitors

After 2015, international guidelines recommend the use of INSTIs instead of NNRTIs or PIs as the third drug in the first-line drug regimen. INSTIs demonstrated advantages in terms of efficacy, tolerability, less drug interactions, and convenience.

Dolutegravir (DTG) is a second-generation INSTI that has been recommended as a preferred first-line regimen in the current guidelines from the Department of Health and Human Services (DHHS), International AIDS Society (IAS), European AIDS Clinical Society (EACS), and World Health Organization (WHO). This recommendation is based on data showing its high efficacy, high genetic barrier to resistance, and minimal drug interaction.

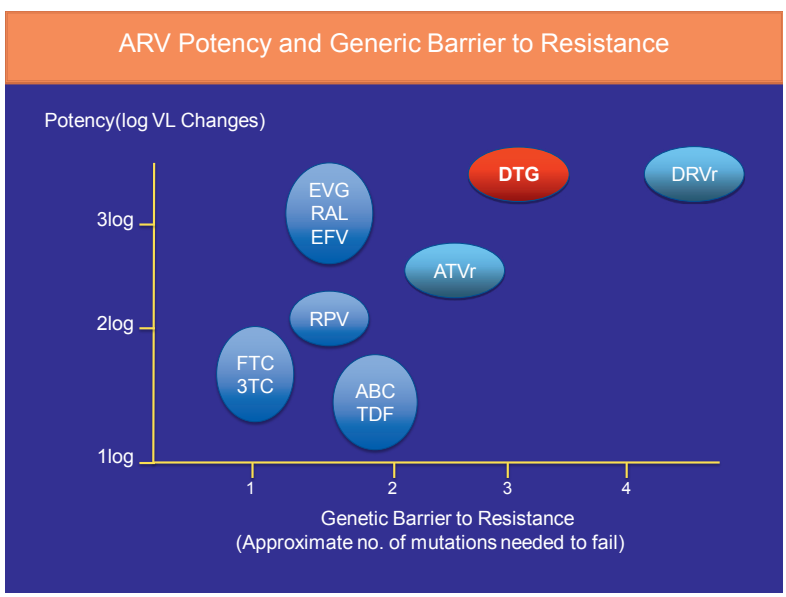

Figure 3 Key Features of Dolutegravir, including its efficacy and high genetic barrier to resistance

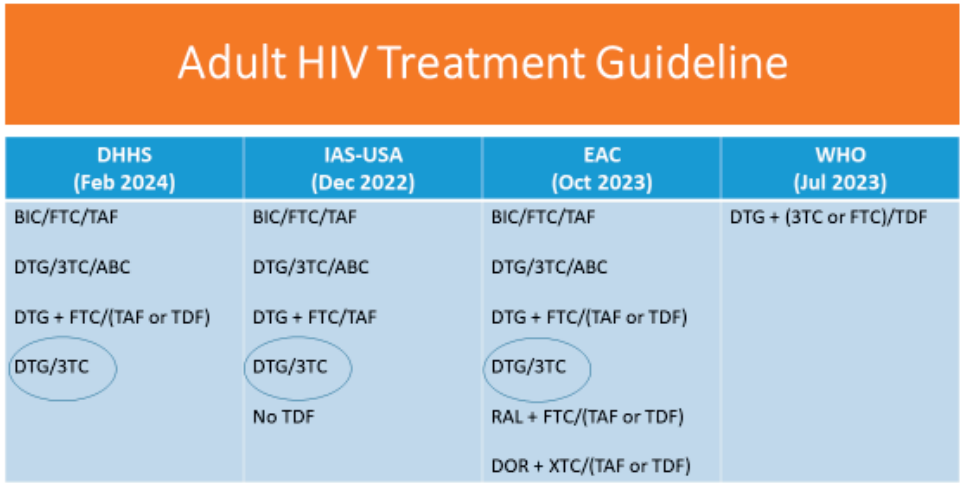

Figure 4 First-line Antiretroviral Therapy according to the 2021-2022 Antiretroviral Therapy Guidelines

Current DHHS Guidelines, Dolutegravir-based regimens are recommended as first-line drugs. Similarly, Thailand's national guidelines also designate Dolutegravir as a preferred first-line drug. Dolutegravir is available in both 50 mg individual tablets and as part of the single tablet regimen TLD (Tenofovir 300 mg, Lamivudine 300 mg, Dolutegravir 50 mg), which is taken as one tablet once daily.

Special considerations for using DTG include:

1. Important Drug-Drug Interactions:

1.1 DTG with antacids containing aluminum or magnesium: DTG can form complexes with Mg^{++} and Al^{+++}, leading to a reduction in DTG levels.[4,5] Studies had shown that DTG should be taken either 2 hours before or 6 hours after antacid intake, to ensure adequate DTG levels.

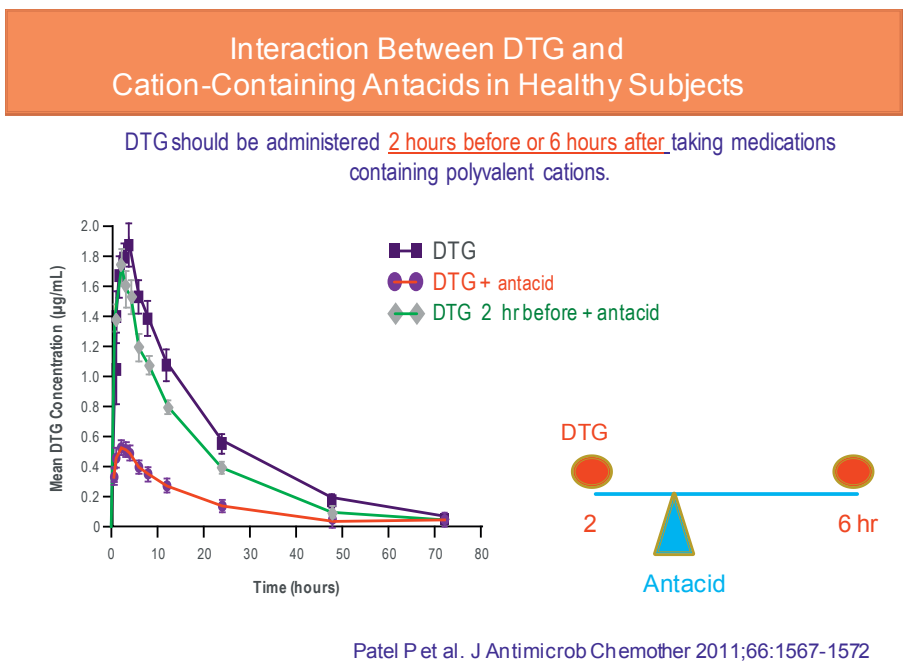

Figure 5 Interaction between DTG and cations in acid-reducing medications

1.2 DTG with food or medications containing calcium, iron, or multivitamins: [4,5] DTG levels in the blood may decrease. To address this, it is recommended to take calcium, iron, or multivitamins along with DTG and with food to ensure sufficient DTG levels for effective viral suppression.

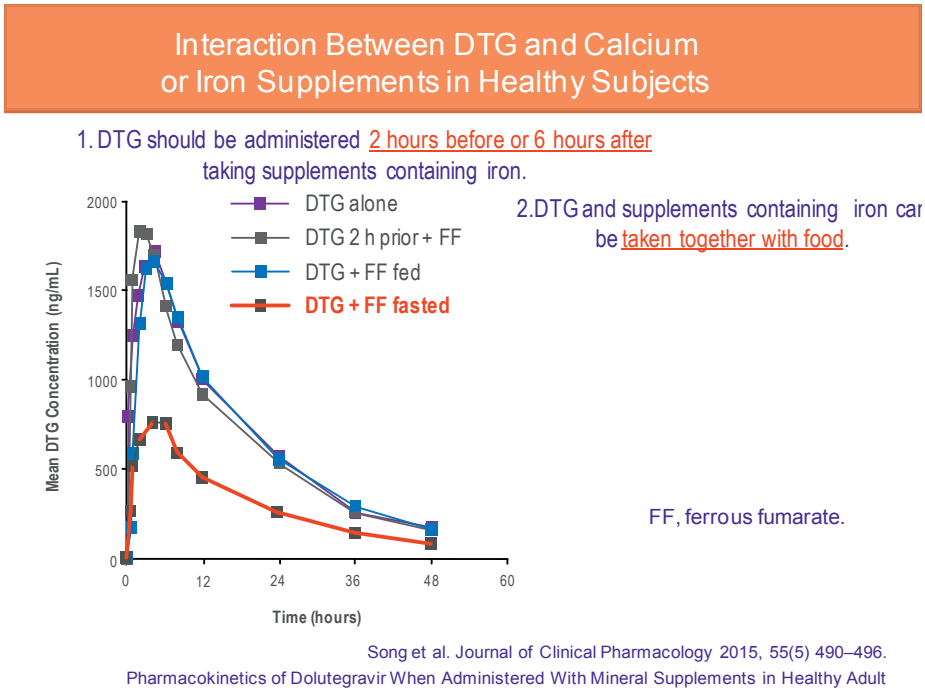

Figure 6 Interaction between DTG and ferrous

1.3 DTG with Metformin:[6,7] Metformin is excreted via the urine through Organic Cation Transporters 2 (OCT2). DTG inhibits the function of OCT2 in the kidneys, leading to reduced excretion of metformin. This results in higher levels of metformin in the plasma. When co-administered, caution is advised due to potential impacts on blood sugar levels, and potential adverse drug reaction of metformin. Consider adjusting metformin dosage to maximal 1 g/day to avoid the risk of lactic acidosis.

Concomitant Drug	Effect on Concentration of DTG	Clinical Comment
metformin	DTG 50 mg. OD Metformin • AUC increases 79% • Cmax increases 66% DTG 50 mg. BID • AUC increases 145% • Cmax increases 111%	• Increase metformin plasma concentration • Consider metformin dose adjustment when starting and stopping DTG

1.4 DTG with antiepileptic drugs:[8]

Phenyltoin is induced by UGT1A1 and CYP3A, which reduces DTG levels. There is no clear study on dosage adjustment. The US guidelines advises against co-administration, while European guidelines recommends adjusting DTG to one tablet twice daily until two weeks after discontinuing antiepileptic drugs.

2. **DTG can increase serum creatinine levels,** particularly in the early initiation because it inhibits the function of Organic Cation Transporter 2 (OCT2), reducing the secretion of creatinine from renal tubular cells, leading to decreased excretion of creatinine into the urine. This can result in a rise in serum creatinine levels by approximately 0.1-0.15 mg/dl for up to 2 weeks after initiation, and these elevated levels may persist for around 48-96 weeks.

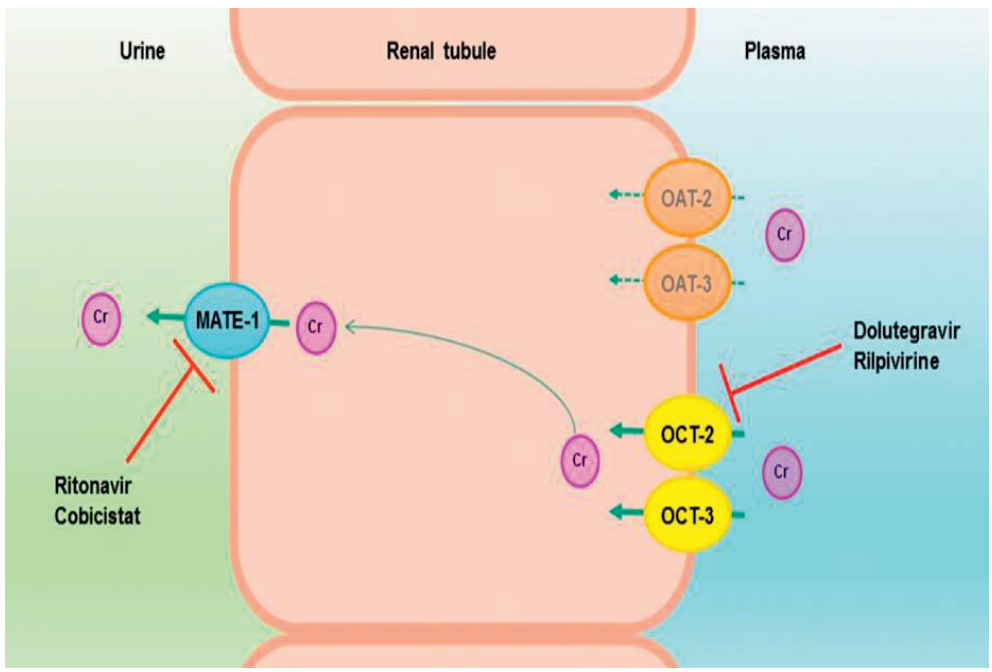

Figure 7 Dolutegravir inhibits the function of Organic Cation Transporter 2, reducing the excretion of creatinine from plasma to urine

3. **DTG adverse reactions:** DTG may interact with various systems, leading to symptoms including[9,10]

Neurological Disorders	
Very common (>1/10)	Headache
Common (<1/10 - >1/100)	Dizziness
Psychiatric Disorders	
Common (<1/10 - >1/100)	Insomnia, anxiety, abnormal dreams, depression
Gastrointestinal Disorders	
Very common (>1/10)	Nausea, diarrhea
Common (<1/10 - >1/100)	Vomiting, flatulence, abdominal pain

4. **The use of DTG during pregnancy:** In early observational studies report an increased incidence of neural tube defects when using DTG during early pregnancy, particularly in the first trimester. Consequently, there was a recommendation against using DTG in pregnant women. However, with more evidence, it was found that the incidence did not differ significantly from the general population. Therefore, after 2019, both DHHS and WHO guidelines permit the use of DTG in reproductive-age women and during pregnancy.[11]

5. **The use of DTG as a first-line 2-drug regimen** has been studied since 2016. GEMINI 1 & 2 studies compared the use of 3TC and DTG in 716 participants, with 3TC, TDF, and DTG in 717 participants, following them for 144 weeks. There were no significant differences in treatment efficacy, viral suppression, and possibly better in reducing TDF-related complications in elderly patients or those with underlying renal dysfunction.[12] Therefore, in 2021, the use of 3TC and DTG as a first-line regimen has been endorsed.

Summary

In 2021, the National AIDS Program in Thailand aligned its antiretroviral therapy guidelines with recommendations from the Department of Disease Control. This resulted in a transition of the first-line drug regimen from 3TC, TDF, EFV to 3TC, TDF, DTG. Moreover, for patients with drug resistance, protease inhibitors have been substituted with INSTIs. Therefore, healthcare professionals, including doctors and nurses, responsible for HIV/AIDS patient care, must possess accurate and comprehensive knowledge of Dolutegravir-based regimens.

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