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Latest advances in the efficacy, tolerability, and monotherapy of integrase inhibitors

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Summary **More than 30 drugs for antiretroviral therapy (ART), including integrase inhibitors (INIs), have been approved by the U.S. Food and Drug Administration (FDA) as of 2017. Integrase is the third essential enzyme in the cycle of human immunodeficiency virus (HIV) replication. INIs can effectively inhibit the replication of HIV and HIV is less prone to develop resistance to INIs clinically. Previous studies based on 7 phase III clinic trials indicate that INIs have satisfactory efficacy and tolerability in patients infected with HIV. The latest advances in INIs indicate that: *i*) dolutegravir (DTG)-based regimens are more efficacious, tolerable, and safer forms of first-, second-, and third-Line ART; *ii*) current studies have indicated that DTG monotherapy fails both virologically and clinically; and *iii*) whether the most cost-effective treatment for DTG is to replace efavirenz (EFV) as a first-line ART, to replace protease inhibitors (PIs) in second-line ART, or to replace both as a monotherapy is unclear. Given these circumstances, further study of INIs in terms of drug interactions, dose reduction, drug convenience, and drug costs is warranted.**

Keywords: Dolutegravir; drug resistance; monotherapy; antiretroviral therapy

1. Introduction

Due to the complexity and lethality of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), a total of 36.7 million people are living with HIV and 1.8 million people worldwide were initially infected with HIV in 2016; there were a total of 708,158 people with HIV/AIDS and 219,050 AIDS-related deaths in China as of May 31, 2017 (*1*-*2*).

Antiretroviral therapy (ART) is a chronic suppressive treatment that effectively provides lifelong treatment for patients with HIV, improving their quality of life (*3*). In 2015, the World Health Organization (WHO) recommended that ART should be initiated in all HIV-infected adults, regardless of their $CD4^+$ cell count (*4*). Because of the expanded scale of ART worldwide, AIDS-related deaths declined by 48% from a peak of 1.9 million in 2005 to 1.0 million in 2016 (*5*).

Since zidovudine (AZT) was used as the first drug for treatment of AIDS in 1987, more than 30 drugs have been approved by the U.S. Food and Drug Administration (FDA) for ART as of 2017. These include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INs), fusion inhibitors (FIs), entry inhibitors (EIs), HIV integrase strand transfer inhibitors (INSTIs), and multi-class combination products (Table 1) (*6*).

Integrase is the third essential enzyme in the cycle of HIV replication. INIs can effectively inhibit the replication of HIV. The drugs mainly used in initial ART at present are NRTIs, NNRTIs, and PIs, but HIV mutates and develops resistance to these drugs. In contrast, HIV is less prone to develop resistance to INIs clinically (*7*-*8*). Functional analogues of integrase have yet to be identified in the human body thus far, so integrase has become an ideal new target for anti-HIV therapy, ushering in an era of ART using INIs (*9*).

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Table 1. Anti-HIV drugs approved by the U.S. FDA over the past 30 years

Approved In	Brand Name	Generic Name	Manufacturer
Nucleoside reverse transcriptase inhibitors (NRTIs)			
1987	Retrovir	Zidovudine (AZT) + Zidovudine (ZDV)	GlaxoSmithKline
1991	Videx	Didanosine (ddI)	Bristol-Myers Squibb
1992	Hivid	Zalcitabine (ddC)	Roche Pharmaceuticals
1994	Zerit	Stavudine (d4T)	Bristol-Myers Squibb
1995	Epivir	Lamivudine (3TC)	GlaxoSmithKline
1997	Combivir	3TC + AZT	GlaxoSmithKline
1998	Ziagen	Abacavir (ABC)	GlaxoSmithKline
2000	Trizivir	ABC + 3TC + AZT	GlaxoSmithKline
2000	Videx EC	ddI	Bristol-Myers Squibb
2001	Viread	Tenofovir Disoproxil Fumarate (TDF)	Gilead Sciences
2003	Emtriva	Emtricitabine (FTC)	Gilead Sciences
2004	Epzicom	ABC + 3TC	GlaxoSmithKline
2004	Truvada	FTC + TDF	Gilead Sciences
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
1996	Viramune	Nevirapine (NVP)	Boehringer Ingelheim
1997	Rescriptor	Delavirdine (DLV)	Pfizer
1998	Sustiva	Efavirenz (EFV)	Bristol-Myers Squibb
2008	Intelence	Etravirine (ETR)	Tibotec
2011	Viramune XR	NVP	Boehringer Ingelheim
2011	Edurant	Rilpivirine (RPV)	Tibotec
Protease inhibitors (PIs)			
1995	Invirase	Saquinavir (SQV)	Roche Pharmaceuticals
1996	Norvir	Ritonavir (RTV)	Abbott Laboratories
1996	Crixivan	Indinavir (IDV)	Merck
1997	Viracept	Nelfinavir (NFV)	Pfizer
1997	Fortovase	SQV Mesylate	Roche Pharmaceuticals
1999	Agenerase	Amprenavir (APV)	GlaxoSmithKline
2000	Kaletra	Lopinavir and Ritonavir (LPV/r)	Abbott Laboratories
2003	Reyataz	Atazanavir (ATV)	Bristol-Myers Squibb
2003	Lexiva	Fosamprenavir (FPV)	GlaxoSmithKline
2005	Aptivus	Tipranavir (TPV)	Boehringer Ingelheim
2006	Prezista; Prezcobix	Darunavir (DRV)	Tibotec
Integrase inhibitors (INIs)			
2007	Isentress	Raltegravir (RAL)	Merck
2012	Stribild	Elvitegravir (EVG)	Gilead Sciences
2013	Tivicay	Dolutegravir (DTG)	GlaxoSmithKline & Shionogi Pharma
Fusion inhibitors (FIs)			
2003	Fuzeon	enfuvirtide, T-20 (ENF)	Roche Pharmaceuticals & Trimeris
Entry inhibitor (EI) - CCR5 co-receptor antagonists			
2007	Selzentry; Celsentri	Maraviroc (MVC)	Pfizer
HIV integrase strand transfer inhibitors (INSTIs)			
2007	Isentress	RAL	Merck & Co.
2013	Tivicay	DTG	ViiV Healthcare
2014	Vitekta	EVG	Gilead Sciences
Multi-class combination products			
2006	Atripla	EFV+FTC+TDF	Gilead Sciences
2011	Complera	FTC+RPV+TDF	Gilead Sciences
2012	Stribild	EVG+Cobicistat+FTC+TDF	Gilead Sciences
2015	Evotaz	ATV Sulfate+Combicistat	Bristol-Myers Squibb
2015	Prezcobix	Cobicistat + DRV Ethanolate	Janssen Pharmaceuticals

2. Clinical trial on INIs, and dolutegravir (DTG) in particular

At the current point in time, 7 clinical trials have demonstrated that INIs, and DTG in particular, has satisfactory efficacy and tolerability in newly diagnosed patients, treated patients, and patients receiving multiple regimens (Table 2).

Walmsley *et al*. conducted a randomized controlled trial (RCT) that divided 833 untreated patients with HIV into a DTG group and an efavirenz (EFV) group. Results indicated that DTG plus abacavir (ABC)-lamivudine (3TC) was significantly superior to EFV-tenofovir (TDF)-emtricitabine (FTC) at 48, 96, and 144 weeks, with better tolerability and fewer dropouts (*10-12*).

Raffi *et al*. conducted an RCT that divided 822 treatment-naive patients with HIV into a DTG group and an Raltegravir (RAL) group. Results indicated that once-daily DTG was comparable to twice-daily RAL in untreated patients in week 48 and week 96 (*13-15*).

Table 2. Efficacy and tolerability of INIs in 7 clinical trials

Authors	Study Design	Sample Size	Group	Drug Dose	Treatment Stage	Primary End Point	Outcomes	Tolerability*	*Ref.*
Walmsley SL, *et al.*	Randomized, double-blind, phase 3 study.	414 419	DTG-ABC-3TC EFV-TDF-FTC	Once daily Once daily	Initial treatment	HIV-1 RNA level of less than 50 copies per milliliter in week 48.	88% 88%	4% 10%	(*17-19*)
Raffi F, *et al.*	Phase 3, randomized, double-blind, active-controlled, non-inferiority study.	411 411	DTG RAL	50 mg once daily 400 mg twice daily	Initial treatment	Proportion of participants with HIV-1 RNA less than 50 copies per mL at 48 weeks with a 10% non-inferiority margin.	88% 85%	2% 2%	(*20-22*)
Feinberg J, *et al.*	Open-label, phase 3b, non-inferiority study.	242 242	DTG + 2 NRTIs DRV plus RTV + 2 NRTIs	50 mg once daily 800 mg plus 100 mg once daily,	Initial treatment	Proportion of patients with HIV-1 RNA concentration lower than 50 copies per mL in week 48 with a 12% non-inferiority margin.	90% 83%	2% 4%	(*23-24*)
Cahn P, *et al.*	Phase 3, randomized, double-blind, active-controlled, non-inferiority study.	354 361	DTG RAL	50 mg once-daily 400 mg twice-daily	Second- or third-line treatment	Proportion of patients with plasma HIV-1 RNA less than 50 copies per mL in week 48.	71% 64%	– –	(*25*)
Nichols G, *et al.*	Single-arm, open-label phase III study.	183	DTG while continuing a failed regimen (without RAL or EVG) through day 7	50 mg	Multiple treatments	*i*) Mean change from baseline in plasma HIV-1 RNA on day 8. *ii*) Proportion of subjects with HIV-1 RNA <50 c/mL in week 24.	-1.43 log10 c/mL 69%	–	(*26*)
Trottier B, *et al.*	Randomized, open-label, Phase IIIb study.	275 278	Early s witch group Late switch group	ABC/DTG/3TC once daily for 48 weeks Continue ART for 24 weeks and then switch to ABC/DTG/3TC	Second- or third-line treatment	Proportion of subjects with HIV-1 RNA <50 copies/ml in week 24.	85% 88%	– –	(*27*)
Orrell C, *et al.*	Randomised, open-label, multicenter, active-controlled, parallel-group, non-inferiority phase 3b study.	250 249	DTG+ABC+3TC ATV+TDF+ FTC	Once a day once a day	Second- or third-line treatment	Proportion of participants with HIV-1 RNA viral loads of less than 50 copies per mL in week 48.	82% 71%	11% 13%	(*28*)

*Treatment discontinuation due to adverse events.

Once-daily dosing with no need for a pharmacokinetic booster makes DTG-based therapy an attractive treatment option for treatment-naive patients infected with HIV-1.

Feinberg *et al*. conducted an RCT that divided 484 therapy-naive adults into a DTG group and a darunavir plus ritonavir (DRV/r) group (*16-17*). Results indicated that once-daily DTG was superior to once-daily DRV/r. Once-daily DTG in combination with fixed-dose NRTIs represents an effective new treatment option for treatment-naive patients infected with HIV-1.

Cahn *et al*. conducted an RCT that divided 719 INI-naive adults with resistance to at least two classes of drugs into a DTG group and an RAL group (*18*). Results indicated that once-daily DTG was well-tolerated and had a greater virological effect than twice-daily RAL in patients who had previously been treated.

Nichols *et al*. conducted a RCT in which 183 adults with resistance to RAL and/or EVG received DTG 50 mg twice daily while continuing their failing regimen through day 7, after which the regimen was optimized with ≥ 1 fully active drug and continued administration of DTG (*19*). Results indicated that the mean change in HIV-1 RNA on day 8 decreased from the baseline and that HIV-1 RNA was < 50 c/mL in 69% of subjects in week 24. DTG 50 mg twice daily therapy was effective in this highly treatment-experienced population with INI-resistant virus.

A study by Trottier *et al*. randomly assigned subjects to switch to ABC/DTG/3TC once daily for 48 weeks (early-switch group) or to continue current ART for 24 weeks and then switch to ABC/DTG/3TC (late-switch group) (*20*). Data revealed that switching to ABC/DTG/3TC was a comparable alternative to continuing ART support ABC/DTG/3TC when considering whether to switch regimens in HIV-1-infected adults with stable viral suppression.

Subjects in the study by Orrell *et al*. were randomly assigned to a DTG group or an atazanavir (ATV) group (*21*). The regimen that included DTG had comparable efficacy and a similar safety profile to the ATV regimen, substantiating the use of DTG to treat HIV-1 infection in treatment-naive women.

Based on international guidelines and the large clinical trials mentioned earlier (*22-24*): *i*) most international guidelines recommend DTG as an integral part of initial treatment; *ii*) data from a number of clinical trials support the use of DTG, which has a high level of antiviral efficacy; *iii*) DTG is administered once daily in a small dose with no need for synergistic action of other drugs and can be administered at any time; *iv*) DTG interacts little with commonly used drugs; and *v*) HIV is unlikely to develop resistance to DTG.

Although the above studies have indicated the advantages of INIs (and especially DTG), there are still many problems with the tolerability and independent use of INIs. These issues were touched upon by national experts and researchers at the 9th International AIDS Society Conference on HIV Science (IAS 2017).

3. Latest advances in INIs according to IAS 2017

Efficacy as initial treatment. Taiwo *et al*. conducted a clinic trial of once-daily DTG (50 mg) + 3TC (300 mg) in treatment-native participants who were infected with HIV-1 and who had a viral load (VL) ≥ 1,000 and < 500,000 copies/mL (*25*). Results indicated that the median change in the CD4 count from entry to week 24 was +167 (86,275) cells/mm3, which means once-daily DTG plus 3TC was efficacious and welltolerated. However, an RCT of this regimen versus standard treatment is warranted.

Figueroa *et al*. conducted a pilot study to evaluate the antiviral efficacy of a dual therapy regimen with DTG plus 3TC as initial ART in 20 treatment-native adults infected with HIV-1 (*26*). Results indicated that there were no new virologic failures, no new AIDS-defining illnesses, and no treatment discontinuations through the extension phase. Dual therapy with DTG plus 3TC was efficacious and tolerated through 96 weeks of treatment, so this approach is being examined in a large randomized, doubleblinded trial.

Efficacy as second- or third-line treatment. Aboud *et al*. published interim data from the DAWNING study, which is a non-inferiority study of DTG plus 2 NRTIs compared to lopinavir/ritonavir (LPV/r) plus 2 NRTIs as second-line treatment (*27*). Results indicated that HIV-1 RNA was < 50 c/mL in 78% of subjects on DTG versus 69% of those on LPV/r in week 24. The Independent Data Monitoring Committee (IDMC) recommended discontinuation of the LPV/r arm due to the superior efficacy of DTG+2NRTIs and the potential of LPV/r to harm subjects based on available data. These findings provide important information to help guide second-line treatment decisions in resource-limited settings.

Moh *et al*. conducted the ANRS 12269 THILAO study to evaluate the efficacy of a third-line treatment based on TDF plus RAL regimen at 48 weeks in HIV-infected adults in sub-Saharan Africa who failed to respond to a second-line protease inhibitor-based regimen (*28*). Of 44 patients who received the TDF 3TC/FTC-NNRTI regimen, 27 had a viral load < 50 copies/ml. The third-line regimen of TDF plus RAL is highly efficient as salvage therapy.

Tolerability. Anstett *et al*. hypothesized that the R263K substitution interferes with some actions of integrase by dysregulating the acetylation of nearby residues (*29*). That study is the first to describe how post-translational modifications affect the drug resistance of HIV. The study's results indicated that HIV-1 resistance to DTG is modulated by epigenetic signals, suggesting that some drugresistant viruses may respond differently to histone deacetylase inhibitors.

Pham *et al*. evaluated mutations associated with INI resistance by sequencing the virus both prior to and at the time of virologic failure (*30*). That study found that virological failure involving DTG monotherapy can occur due to replication of a virus containing a novel S230R substitution that confers a modest level of resistance to DTG and other INSTIs.

Monotherapy and virus inhibition. Heredia *et al*. conducted two studies that respectively evaluated the efficacy of 20-week monotherapy with DTG or RAL and dual therapy with DTG plus lamivudine (3TC) in humanized mice (HSC-NSG) infected with HIV_{BaL} (*31*). Results indicated that DTG monotherapy does not maintain HIV suppression, suggesting that streamlining of ART may require dual therapy.

Liang *et al*. studied the status of viral infection during suppression achieved by ART in HIV-positive individuals receiving DTG-based ART (*32*). That study found that patients treated with DTG had more robust levels of antibody-dependent cellular cytotoxicity (ADCC) responses and earlier recovery of neutralization than those treated with EVG. This means that HIV would be less likely to evolve following exposure to DTG.

4. Prospects for the future

As a result of continued efforts by national experts for close to 10 years, INIs have gradually become a new class of ART drugs to manage patients infected with HIV. IAS 2017 highlighted the latest advances in the efficacy, tolerability, and monotherapy of INIs (*32-39*) based on many groundbreaking studies by national experts and researchers: *i*) dolutegravir (DTG)-based regimens are more efficacious, tolerable, and safer forms of first-, second-, and third-Line ART; *ii*) current studies have indicated that DTG monotherapy fails both virologically and clinically; and *iii*) whether the most cost-effective treatment for DTG is to replace efavirenz (EFV) as a first-line ART, to replace protease inhibitors (PIs) in second-line ART, or to replace both as a monotherapy is unclear.

Based on recent studies, further study of INIs in terms of drug interactions, dose reduction, drug convenience, and drug costs is warranted.

Although numerous studies are underway overseas, full clinical trials of INIs and related studies of clinical efficacy involving Chinese samples have yet to be conducted. Clinical trials on INIs in Chinese samples in the "real world" are anticipated.

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