Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

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Product Name:	Viread (tenofovir disoproxil fumarate)
Pediatric Labeling Approval Date:	February 11, 2018
Application Type/Numbers:	NDA 021356, NDA 022577
Applicant:	Gilead Sciences, Inc.
OSE RCM #:	2021-540

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Viread (tenofovir disoproxil fumarate) in pediatric patients through 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on serious, unlabeled adverse events associated with Viread in U.S. pediatric patients.

On October 26, 2001, FDA first approved Viread for the treatment of human immunodeficiency virus-1 (HIV-1) infection, in combination with other antiretroviral products, in adults. On September 25, 2009, the indication was expanded to include the treatment of HIV-1 infection, in combination with other antiretroviral agents, in patients 12 to less than 18 years of age. This supplement was in response to a Pediatric Written Request issued on December 21, 2001. On August 11, 2008, FDA approved a supplement for the treatment of hepatitis B virus (HBV) infection in adults. On January 18, 2012, FDA approved a supplement which further expanded the indication to include treatment of HIV-1 infection in patients 2 to less than 12 years of age. On August 16, 2012, the indication was expanded to include pediatric patients 12 to less than 18 years of age for the treatment of HBV infection. This pediatric postmarketing pharmacovigilance review was prompted by pediatric labeling approved on December 11, 2018, that further expanded the indication to include pediatric patients 2 to less than 12 years of age for the treatment of HBV infection. This supplement was submitted in response to PREA postmarketing requirement (PMR) to assess the safety and efficacy of Viread in the treatment of pediatric patients 2 to less than 12 years of age with chronic HBV infection.

DPV reviewed all U.S. serious FAERS reports with Viread use in the pediatric population (ages 0 through 17 years), received by FDA from June 1, 2014 through March 16, 2021. After exclusions, DPV identified three non-fatal U.S. serious pediatric cases with labeled adverse events of renal impairment, decreased bone mineral density (BMD), and osteopenia, which are adequately described in the Warnings and Precautions section of the Viread labeling. There were no new safety signals identified, no increased severity of any labeled events, and no deaths directly associated with Viread. The reported adverse events are consistent with the known adverse reactions described in the Viread labeling.

This review did not identify any new or unexpected pediatric safety concerns for Viread. DPV will continue to monitor all adverse events associated with Viread use through routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Viread (tenofovir disoproxil fumarate) in pediatric patients through 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Viread in U.S. pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Viread, a nucleotide reverse transcriptase inhibitor, is indicated for the treatment of (1) human immunodeficiency virus-1 (HIV-1) infection, in combination with other antiretroviral agents, in adults and pediatric patients 2 years of age and older weighing at least 10 kg and (2) chronic hepatitis B virus (HBV) infection in adults and pediatric patients 2 years and older weighing at least 10 kg. The recommended dosage of Viread in pediatric patients 2 years and older weighing at least 35 kg is 300 mg orally once daily and for pediatric patients 2 years of age and older weighing at least 10 kg is 8 mg/kg (up to a maximum of 300 mg) orally once daily. The dosage for Viread is the same for both HIV and HBV indications. Approved formulations include a 150, 200, 250, 300 mg tablet [New Drug Application (NDA) 021356] and a 40 mg per 1 gm of oral powder (NDA 022577).[1]

1.1.1 Human Immunodeficiency Virus-1 (HIV-1) Infection.

Viread was first approved on October 26, 2001 for the treatment of HIV-1 infection, in combination with other antiretroviral products, in adults. On September 25, 2009, the Applicant submitted supplemental NDA (sNDA) 021356/S-34 to expand the indication of Viread to include the treatment of HIV-1 infection, in combination with other antiretroviral agents, in patients 12 to less than 18 years of age, based on 48-week clinical data from Study GS-US-104-0321. This supplement was in response to a Pediatric Written Request issued on December 21, 2001. The supplement was approved, and labeling changes were made on March 24, 2010. In addition, a supplement (S-38) was approved on January 18, 2012, which further expanded the indication to include treatment of HIV-1 infection in patients 2 to less than 12 years of age.

The Office of Surveillance and Epidemiology (OSE) previously evaluated postmarketing adverse event reports with a serious outcome for Viread in pediatric patients up to 17 years of age.[2] OSE's evaluation, dated March 15, 2012, was prompted by the pediatric labeling changes on March 24, 2010 and January 18, 2012 that expanded the indication to patients 12 to less than 18 years of age and 2 to less than 12 years of age, respectively. FDA presented OSE's evaluation to the Pediatric Advisory Committee (PAC) on May 7, 2012. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Viread.

1.1.2 Chronic Hepatitis B Infection

On August 11, 2008, FDA approved sNDA 021356/S-025 for the treatment of HBV in adults. On February 17, 2012, the Applicant submitted a sNDA (021356/S-42) to expand the indication

to include pediatric patients 12 to less than 18 years of age for the treatment of HBV infection. This supplement was approved on August 16, 2012.

OSE previously evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Viread in pediatric patients 12 years of age and older.[3] OSE's evaluation, dated July 22, 2014, was prompted by the pediatric labeling changes on August 16, 2012, which was based on the results from Trial GS-US-174-0115. FDA presented OSE's evaluation to the PAC on September 23, 2014. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Viread.

This current review was prompted by pediatric labeling approved on December 11, 2018, that further expanded the indication to include pediatric patients 2 to less than 12 years of age for the treatment of HBV infection based upon the data from Trial GS-US-174-0144. Supplement 57 was submitted in response to PREA postmarketing requirement (PMR) 283-2 to assess the safety and efficacy of Viread in the treatment of pediatric patients 2 to less than 12 years of age with chronic HBV infection.

The following regulatory history was reproduced from Dr. Samer El-Kamary's clinical review for NDA 021356/S-57.[4]

> *Pediatric labeling was based on data from a prospective, randomized, double-blind, placebo-controlled trial to compare the antiviral efficacy, safety, and tolerability of tenofovir to placebo in pediatric patients 2 to less than 12 years of age with chronic HBV infection. One hundred tenofovir-naïve pediatric patients aged 2 to less than 12 years of age with chronic HBV infection, HBV DNA $\geq 10^5$ copies/mL, and either an alanine aminotransferase (ALT) of $\geq$ 2 times the upper limit of normal (ULN) at screening or any history of an ALT $\geq$ 2 times ULN over the past $\leq$ 24 months were eligible for enrollment. These patients were randomized in a 1:1 ratio to treatment arm A (tenofovir orally once daily for 72 weeks) or B (matching placebo orally once daily for 72 weeks). At 72 weeks of blinded randomized treatment, each subject was to be switched to open-label tenofovir treatment for an additional 120 weeks. The primary efficacy endpoint was the proportion of subjects with HBV DNA < 69 IU/mL at Week 48. The study demonstrated that a significantly greater proportion of subjects in the tenofovir group achieved HBV DNA < 69 IU/mL at Week 48 compared with the placebo group (77% vs. 7%). Tenofovir treatment also led to a higher proportion of subjects with ALT normalization at Week 48 than placebo (66% vs. 15%). However, the two treatment groups had similar proportion of subjects with HBeAg loss (30% vs. 28%) or proportion of subjects with HBeAg seroconversion (25% vs. 24%) at Week 48. During the clinical review, it was noticed that efficacy in children 2 years to less than 6 years of age was less than that in children 6 years to less than 12 years of age. Updated data from the Applicant showed that four out of the 10 subjects receiving tenofovir treatment in the less than 6 years old subgroup who were considered treatment failures at Week 48 actually achieved HBV DNA < 69 IU/mL after Week 48. The frequency of serious adverse events was relatively low. The safety issues identified in this study are similar to those previously described in adult and adolescent studies of HBV and HIV patients. A decline in bone mineral density (BMD) in adults and slower gain in*

adolescents is a well-known adverse event associated with tenofovir exposure. Similar to adolescents, patients in both treatment groups gained BMD, but placebo patients gained more than tenofovir patients at each assessment. Overall, tenofovir was well-tolerated for the treatment of chronic HBV in children 2 to less than 12 years of age. No new safety signals were identified.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Viread labeling includes the following safety information (excerpted from the pertinent sections). For further Viread labeling, including dosage and administration for adult patients, please refer to full prescribing information.[1]

Warning: Posttreatment Acute Exacerbation of Hepatitis B

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely in HBV-infected patients who discontinue VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted. *[see Warnings and Precautions (5.1)].*

----------WARNINGS AND PRECAUTIONS----------

Labeling Section	**Adverse Events**
Section 5.1 Severe acute exacerbation of Hepatitis B in patients with HBV infection	• Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis B. • Patients infected with HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.
Section 5.2 New onset or worsening renal impairment	• Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported with the use of VIREAD. • Viread should be avoided with concurrent or recent use of a nephrotoxic agent. Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir. • Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in patients at risk for renal dysfunction.
Section 5.3 Patients coinfected with HIV-1 and HBV	• Due to risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen.
Section 5.4 Immune Reconstitution Syndrome	• Immune reconstitution syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including VIREAD.

Labeling Section	Adverse Events
	• Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.
Section 5.5 Bone loss and mineralization defects	• In HIV-1 infected adults, VIREAD was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. • In HIV-1 infected subjects 2 years to less than 18 years of age, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Similar trends were observed in chronic HBV-infected subjects 2 years to less than 18 years of age. • The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk in adults and pediatric subjects 2 years and older are unknown. • Cases of osteomalacia associated with proximal renal tubulopathy have been reported in association with VIREAD use.
Section 5.6 Lactic acidosis/severe hepatomegaly with steatosis	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir, alone or in combination with other antiretrovirals.
Section 5.7 Risk of adverse reactions due to drug interactions	• The concomitant use of VIREAD and other drugs may result in known or potentially significant drug interactions, some of which may lead to possible clinically significant adverse reactions from greater exposures of concomitant drugs *[see Drug Interactions (7.2)]*.

----------ADVERSE REACTIONS----------

- In HIV-infected adult subjects: Most common adverse reactions (incidence greater than or equal to 10%, Grades 2-4) were rash, diarrhea, nausea, headache, pain, depression, and asthenia. (6.1)
- In HBV-infected subjects with compensated liver disease: Most common adverse reaction (all grades) was nausea (9%). (6.1)
- In HBV-infected subjects with decompensated liver disease: Most common adverse reactions (incidence greater than or equal to 10%, all grades) were abdominal pain, nausea, insomnia, pruritus, vomiting, dizziness, and pyrexia. (6.1)
- In pediatric subjects**:** Adverse reactions in pediatric subjects were consistent with those observed in adults. (6.1)

----------**DRUG INTERACTIONS**----------

- Tenofovir disoproxil fumarate increases didanosine concentrations. Dose reduction and close monitoring for didanosine toxicity are warranted. (7.2)
- Coadministration decreases atazanavir concentrations. When coadministered with VIREAD, use atazanavir given with ritonavir. (7.2)
- Coadministration of VIREAD with certain HIV-1 protease inhibitors or certain drugs to treat HCV increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.2)

----------**USE IN SPECIFIC POPULUATIONS**----------

- Lactation: Breastfeeding in HIV-1 infected mothers is not recommended due to the potential for HIV-1 transmission. (8.2)
- Pediatric Use: The effects of VIREAD-associated changes in bone mineral density (BMD) and biochemical markers on long-term bone health and future fracture risk in chronic HBV-infected pediatric patients 2 years and older are unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients 2 years and older, and in particular, the effects of long-duration exposure in younger children is unknown. Safety and effectiveness of VIREAD in chronic HBV-infected pediatric patients younger than 2 years of age and weighing less than 10 kg have not been established.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*

Date of search	March 17, 2021
Time period of search	June 1, 2014† - March 16, 2021
Search type	Product-Manufacturer Reporting Summary
Product terms	Product Active Ingredient: Tenofovir disoproxil fumarate, tenofovir\tenofovir disoproxil fumarate
MedDRA search terms (Version 23.1)	All Preferred terms (PT)
Search parameters	All outcomes, worldwide

* See Appendix A for a description of the FAERS database.
† FAERS search end date based on previous OSE review completed July 22, 2014 with FAERS data lock dates June 1, 2013 through May 31, 2014.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from June 1, 2014 through March 16, 2021 with Viread.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From June 1, 2014 through March 16, 2021 with Viread			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	9,723 (6,817)	9,235 (6,353)	500 (194)
Pediatrics (0 - <18 years)	180 (37)	174 **(32)**	17 (**6**)

* May include duplicates and transplacental exposures and have not been assessed for causality.
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.

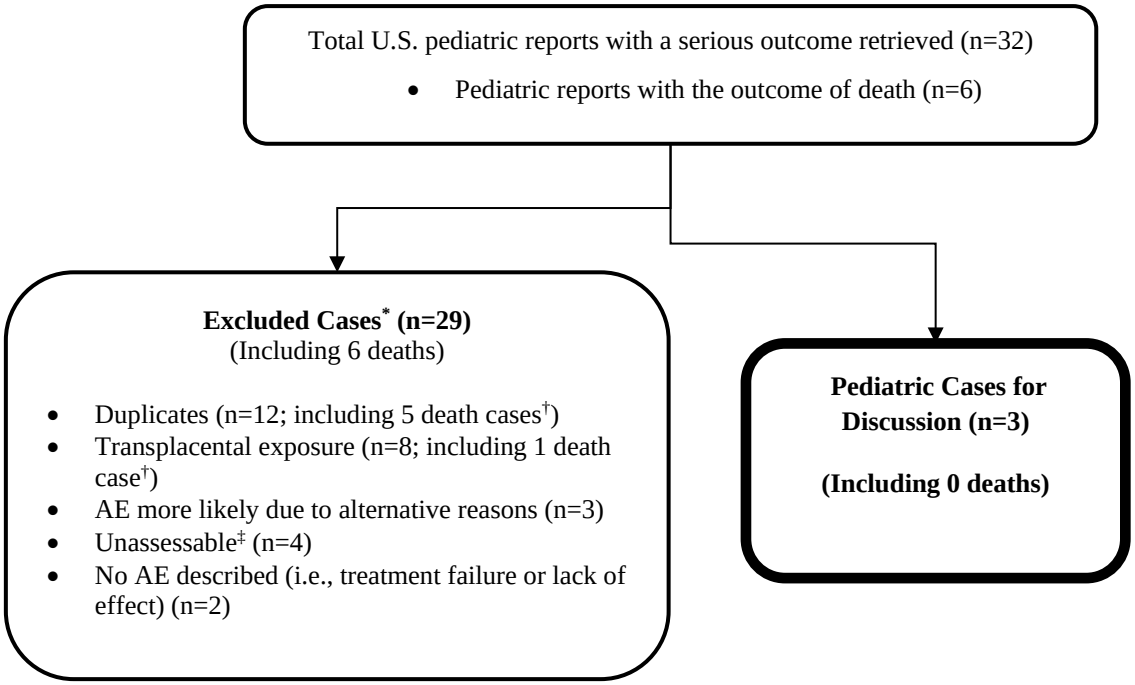
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 32 U.S. serious pediatric reports from June 1, 2014 through March 16, 2021.

We reviewed all FAERS U.S. pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as if the adverse event was more likely due to an alternative cause (n=3; i.e., cellulitis from a fall, fracture from a fall, and fracture in a patient not receiving Viread for at least 5 years), reporting lack of efficacy or did not report an adverse event (n=2), described transplacental exposure (n=8), the report was unassessable due to limited information (n=4), or if the report was a duplicate (n=12). We summarize the remaining cases in the sections below.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Viread



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.

† All reports with a fatal outcome were duplicates of one case. The case reported the death of a premature neonate and small-for-dates baby with transplacental exposure of multiple concomitant antiretroviral therapies.

‡ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the case cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal U.S. pediatric adverse event cases associated with Viread.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=3)

We identified three serious FAERS cases with Viread in the U.S. pediatric population reporting a non-fatal serious outcome. All three cases were litigation reports of labeled adverse events (i.e., increased serum creatinine/renal impairment, decreased BMD, and osteopenia) containing limited clinical information in pediatric patients receiving Viread for the treatment of HIV infection. Appendix B contains a line listing of the three pediatric cases.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with Viread use in the pediatric population (ages 0 through 17 years), received by FDA from June 1, 2014 through March 16, 2021. After exclusions, DPV identified three non-fatal U.S. serious pediatric cases with labeled adverse events of renal impairment, decreased BMD, and osteopenia, which are adequately described in the Warnings and Precautions section. There were no new safety signals identified, no increased severity of any labeled events, and no deaths directly associated with Viread. The reported adverse events are consistent with the known adverse reactions described in the Viread labeling.

5 CONCLUSION

DPV did not identify any new or unexpected pediatric safety concerns for Viread.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of Viread through routine pharmacovigilance.

7 REFERENCES

[1] Viread (tenofovir disoproxil fumarate) [package insert]. Foster City, CA: Gilead Sciences, Inc.; Revised April 2019. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process Accessed on March 30, 2021.
[2] Boxwell D. Viread (tenofovir disoproxil fumarate) Pediatric Postmarketing Adverse Event Review. March 15, 2012. Reference ID: 3104511.
[3] Boxwell D. Viread (tenofovir disoproxil fumarate) Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review. July 22, 2014. Reference ID: 3596985.
[4] El-Kamary. Division of Antiviral Products Medical Officer's Clinical Review of NDA 021356/S-57. November 21, 2018. Reference ID: 4353269.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=3)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	7/30/2019	16648024	3	US-GILEAD-2019-0420430	Non-expedited	13	F	U.S.	OT
2	7/13/2020	18012487	2	US-GILEAD-2020-0479987	Expedited	16	M	U.S.	OT
3	7/7/2020	17989310	2	US-GILEAD-2020-0478426	Expedited	17	M	U.S.	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: OT=other medically significant

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/s/

KIMBERLEY A SWANK
06/08/2021 07:52:58 AM

IVONE E KIM
06/08/2021 08:01:37 AM

RACHNA KAPOOR
06/08/2021 08:51:55 AM

IDA-LINA DIAK
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