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15 UNITED STATES DISTRICT COURT
16 NORTHERN DISTRICT OF CALIFORNIA

17 JAMES RUBEN GREEN, DARRELL WAYNE
18 TERRY, GEROME WILSON, JASON DOYLE
19 DORN, JOHN DOE 14, LINDA COLEMAN,
20 MARQUIS D. GREEN, MELISSA A. WEBB,
SHEILA W. BEARD, STEPHEN JOINER,

21 Plaintiffs,

22 v.

23 GILEAD SCIENCES, INC.,

24 Defendant.

No. _____

COMPLAINT FOR DAMAGES

JURY TRIAL DEMANDED

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1 Plaintiffs bring this civil action for damages against Defendant Gilead Sciences, Inc. (“Gilead”
2 or “Defendant”). Based on the investigation of counsel, Plaintiffs allege on information and belief as
3 follows:

4 **I. NATURE OF THE ACTION**

5 1. This action arises out of injuries Plaintiffs sustained as a result of ingesting one or more
6 of the prescription drugs Viread, Truvada, Atripla, Complera, and Stribild, which are manufactured
7 and marketed by Gilead for the treatment of Human Immunodeficiency Virus-1 (“HIV”) infection.¹

8 2. Gilead designed each of the drugs to contain a form of the compound tenofovir that
9 Gilead knew was toxic to patients’ kidneys and bones. Tenofovir is a nucleotide analogue reverse
10 transcriptase inhibitor (“NRTI”), one of the classes of antiretroviral drugs used to treat HIV. NRTIs
11 work by blocking an enzyme HIV needs to replicate. Gilead did not discover tenofovir. Scientists in
12 Europe discovered tenofovir in the 1980s, and though the anti-HIV properties of tenofovir were
13 promising, it had a downside: it cannot not be administered effectively by mouth.

14 3. Because an intravenous tenofovir formulation had little sales potential, Gilead
15 developed a form of tenofovir, tenofovir disoproxil, which can be taken orally.² The fumaric acid salt
16 of tenofovir disoproxil is tenofovir disoproxil fumarate (“TDF”). When a patient takes a pill containing
17 TDF, the patient’s body converts TDF into tenofovir. Although TDF can be taken by mouth, a high
18 dose of 300 mg is typically required to achieve the desired therapeutic effect.

19 4. Gilead designed TDF 300 mg to be an active ingredient in five drugs that are approved
20 to treat HIV: Viread (TDF 300 mg tablets), approved October 26, 2001; Truvada (TDF 300
21 mg/emtricitabine 200 mg tablets), approved August 2, 2004; Atripla (TDF 300 mg/emtricitabine 200
22 mg/efavirenz 600 mg tablets), approved July 12, 2006; Complera (TDF 300 mg/emtricitabine 200
23 mg/rilpivirine 25 mg tablets), approved August 10, 2011; and Stribild (TDF 300 mg/emtricitabine 200
24

25 ¹ Viread is also indicated to treat Hepatitis B. And Truvada is also indicated for use in combination
26 with safe sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired
HIV-1 in adults at high risk.

27 ² Tenofovir disoproxil is a prodrug form of tenofovir. Prodrugs are pharmacologically inactive
28 compounds that can be more efficiently absorbed into the bloodstream and then converted into the
active form of the drug within the body.

1 mg/elvitegravir 150 mg/cobicistat 150 mg tablets), approved August 27, 2012 (collectively, these are
2 the “TDF Drugs”).

3 5. Before Gilead began selling its first TDF Drug, Viread, in 2001, Gilead knew that TDF
4 posed a safety risk to patients’ kidneys and bones. Gilead knew that two of its other antiviral drugs
5 with structures similar to tenofovir, cidofovir and adefovir dipivoxil, had been highly nephrotoxic (i.e.,
6 toxic to kidneys) and that preclinical data for TDF showed that it could cause significant kidney and
7 bone damage. Gilead also knew that the relatively high dose of TDF created a greater risk of toxic
8 effects, and that bone and kidney toxicities were even more likely to be seen with long-term use of
9 TDF for the treatment of a virus that, for the foreseeable future, has no cure.

10 6. Gilead’s knowledge of the toxic effects of TDF only grew as patients began treatment
11 with and were injured by each successive TDF product. By the time Gilead designed Stribild, it had
12 ten years’ worth of cumulative evidence that TDF injured patients’ kidneys and bones.

13 7. Gilead also knew, before it obtained approval to market Viread and Gilead’s subsequent
14 TDF Drugs, that it had discovered a safer tenofovir prodrug, tenofovir alafenamide fumarate (“TAF”).
15 TAF is absorbed into the cells HIV targets much more efficiently than TDF. As a result, TAF can be
16 administered at a dramatically reduced dose compared to TDF, but still achieve the same or higher
17 concentrations of active tenofovir in the target cells. Because TAF can be administered at a much lower
18 dose than TDF, its use is associated with less toxicity and fewer side effects. A 25 mg dose of TAF
19 achieves the same therapeutic effect as a 300 mg dose of TDF, with a better safety profile. Despite
20 knowing that TAF could be given at a much lower, safer dose, Gilead designed Viread, Truvada,
21 Atripla, Complera, and Stribild to contain TDF rather than safer TAF.

22 8. Falsely claiming that TAF was not different enough from TDF, Gilead abruptly shelved
23 its TAF design in 2004. However, as John Milligan, Gilead’s President and Chief Executive Officer,
24 later admitted to investment analysts, the real reason Gilead abandoned the TAF design was that TAF
25 was *too different* from TDF. Once Gilead’s first TDF product, Viread, was on the market, Gilead did
26 not want to hurt TDF sales by admitting that its TDF-based products are unreasonably and
27 unnecessarily unsafe.

28

1 9. It was crucial at that time for Gilead to increase Viread sales, which comprised 53% of
2 Gilead’s total product sales in 2002, and 68% of Gilead’s total product sales in 2003. Gilead was so
3 desperate to expand Viread sales that when promoting the drug to doctors, it called Viread a “miracle
4 drug” with “no toxicities.” Gilead did not tell doctors the facts: that Viread posed significant risks to
5 patients’ kidneys and bones.

6 10. In addition, Gilead knew that by withholding the safer TAF design, it could extend the
7 longevity of its HIV drug franchise and make billions two times over: first, with TDF medications
8 until TDF patent expiration, which would begin by no later than 2018, and second, with TAF
9 medications until TAF patent expiration as late as 2032. Only once Gilead realized billions in sales
10 through most of the TDF patent life did it seek to market safer TAF-based versions of its HIV
11 medications.

12 11. Finally, in 2015, Gilead began selling the first of its TAF-designed medicines and
13 convinced doctors to switch their patients from TDF-based to TAF-based regimens by demonstrating
14 TAF’s superior safety profile over TDF with respect to kidney and bone toxicity—the very benefits
15 that Gilead could have and should have incorporated into its prior product designs but withheld from
16 doctors and patients for over a decade.

17 12. Gilead also made Stribild even more dangerous to Plaintiffs when it designed the drug
18 to include cobicistat in combination with 300 mg TDF. Cobicistat is a pharmacoenhancer or “booster”
19 that inhibits the breakdown of elvitegravir, another active ingredient in Stribild. Cobicistat allows
20 elvitegravir to persist in the patient’s system long enough to permit once-daily dosing.

21 13. Gilead knew years before it developed Stribild that: (a) higher tenofovir concentrations
22 in patients’ blood, as opposed to the target cells, endangers the kidneys; (b) tenofovir concentrations
23 in patients’ blood increase significantly when patients take tenofovir with a booster; and (c) TDF-
24 associated renal toxicity occurs more frequently in patients taking TDF as part of a boosted regimen.

25 14. When Gilead developed its first TAF-based antiviral product, Genvoya—which is
26 Stribild with TAF in place of TDF—Gilead reduced the dose of TAF from 25 mg to 10 mg to account
27 for the fact that cobicistat significantly increases tenofovir concentrations. Gilead knew to reduce the
28 dose of TAF in Genvoya before it submitted Stribild to the FDA for marketing approval. Despite this

1 knowledge, Gilead did not reduce the dose of TDF when it designed Stribild. Stribild is even more
2 toxic to patients' kidneys and bones than Gilead's other TDF-based products.

3 15. In addition to withholding safer designs, Gilead failed to adequately warn physicians
4 and patients about the risks and safe use of TDF. Gilead provided only the weakest, inadequate
5 warnings to doctors and patients about the need for frequent monitoring of all patients for TDF-
6 associated kidney and bone damage—preventing doctors from detecting early signs of TDF toxicity.

7 16. Gilead provides stronger monitoring warnings to physicians and patients in the
8 European Union (EU) than it does in the United States for the exact same TDF products. Contrary to
9 its U.S. labeling, Gilead has consistently recommended, since the approval of its first TDF Drug in the
10 EU, that doctors in the EU monitor all TDF Drug patients for multiple markers of TDF toxicity on a
11 frequent, specified schedule. There is no scientific or medical rationale for these differences. Gilead
12 was more concerned with increasing or maintaining crucial U.S. sales than it was in safeguarding
13 patients from the known risks of TDF.

14 17. Gilead could have strengthened the warnings in its U.S. labels at any time, including
15 before FDA approval for all TDF Drugs and after FDA approval for Viread, Truvada, Atripla, and
16 Complera. After August 2008 through July 2012, Gilead could have unilaterally strengthened the
17 warnings in its TDF Drug labels after approval based on: increasing evidence that patients with and
18 without preexisting risk factors were experiencing adverse effects with a frequency and severity greater
19 than reported in Gilead's Viread clinical trials; expanding evidence that all patients are at risk for TDF-
20 induced nephrotoxicity; and Gilead's own determinations to give stronger warnings regarding the
21 exact same TDF Drugs in the EU. This post-approval information demonstrated risks of a different
22 frequency and severity than information previously presented to the FDA.

23 18. Gilead intentionally withheld a safer alternative design of TDF Drugs it knew to be
24 dangerously toxic to patients' kidneys and bones, while failing to adequately warn about the risks and
25 safer use of the defective drugs, solely to make more money. Accordingly, Plaintiffs bring this action
26 to recover damages for their personal injuries and seek punitive damages arising from Gilead's willful
27 and wanton conduct.

1 **II. JURISDICTION AND VENUE**

2 19. Jurisdiction exists under 28 U.S.C. § 1332(a) because all Plaintiffs and Gilead are
3 citizens of different states and the matter in controversy exceeds the sum or value of \$75,000, exclusive
4 of interests and costs.

5 20. Venue is proper in this District under 28 U.S.C. § 1391(1)–(2). Defendant resides in
6 this District and a substantial part of the events and omissions giving rise to Plaintiffs’ claims occurred
7 in this District.

8 **III. INTRADISTRICT ASSIGNMENT**

9 21. Pursuant to Civil L.R. 3-2(c), this action shall be assigned to the San Francisco Division
10 or the Oakland Division because Gilead resides and has its principal place of business in San Mateo
11 County. This action is related to another action pending before Judge Jon S. Tigar in the Northern
12 District of California.

13 **IV. PARTIES**

14 22. Plaintiffs are consumers who ingested one or more of the following TDF Drugs: Viread,
15 Truvada, Atripla, Complera, or Stribild.

16 23. Plaintiffs suffered personal injuries caused by ingesting TDF.

17 24. Plaintiff James Ruben Green is and was at all relevant times a citizen of the State of
18 Texas and domiciled in Houston, Texas. Plaintiff James Ruben Green purchased and ingested the
19 following TDF Drugs for an FDA-approved use of the drugs: Truvada and Complera beginning in
20 2011. As a result of Gilead’s wrongful conduct with respect to the defective TDF Drugs, Plaintiff
21 ingested and was injured by the foregoing TDF Drugs. Plaintiff’s ingestion of the TDF Drugs caused
22 and/or contributed to Plaintiff suffering bone demineralization, which resulted in a diagnosis of
23 weakening of the bones. Plaintiff required and incurred and will continue to require and incur expenses
24 in connection with medical treatment as a result of these injuries. Plaintiff has endured and will
25 continue to endure pain, suffering, mental anguish, and loss of enjoyment of life as a result of his
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1 injuries, has suffered lost earnings and/or a loss of earning capacity, and other injuries and damages to
2 be proven at trial.

3 25. Plaintiff Darrell Wayne Terry is and was at all relevant times a citizen of the State of
4 Alabama and domiciled in Brighton, Alabama. Plaintiff Darrell Wayne Terry purchased and ingested
5 the following TDF Drug for an FDA-approved use of the drug: Truvada beginning in 2004. As a result
6 of Gilead's wrongful conduct with respect to the defective TDF Drug, Plaintiff ingested and was
7 injured by the foregoing TDF Drug. Plaintiff's ingestion of the TDF Drug caused and/or contributed
8 to Plaintiff suffering bone demineralization, which resulted in a diagnosis of osteoporosis. Plaintiff
9 Darrell Wayne Terry required and incurred and will continue to require and incur expenses in
10 connection with medical treatment as a result of these injuries. Plaintiff has endured and will continue
11 to endure pain, suffering, mental anguish, and loss of enjoyment of life as a result of his injuries, has
12 suffered lost earnings and/or a loss of earning capacity, and other injuries and damages to be proven
13 at trial.

14
15
16 26. Plaintiff Gerome Wilson is and was at all relevant times a citizen of the Commonwealth
17 of Virginia and domiciled in Ruckersville, Virginia. Plaintiff Gerome Wilson purchased and ingested
18 the following TDF Drug for an FDA-approved use of the drug: Atripla beginning in 2008. As a result
19 of Gilead's wrongful conduct with respect to the defective TDF Drug, Plaintiff ingested and was
20 injured by the foregoing TDF Drug. Plaintiff's ingestion of the TDF Drug caused and/or contributed
21 to Plaintiff suffering bone demineralization, which resulted in a diagnosis of osteoporosis. Plaintiff
22 Gerome Wilson required and incurred and will continue to require and incur expenses in connection
23 with medical treatment as a result of these injuries. Plaintiff has endured and will continue to endure
24 pain, suffering, mental anguish, and loss of enjoyment of life as a result of his injuries, has suffered
25 lost earnings and/or a loss of earning capacity, and other injuries and damages to be proven at trial.
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1 27. Plaintiff Jason Doyle Dorn is and was at all relevant times a citizen of the State of
2 Connecticut and domiciled in West Haven, Connecticut. Plaintiff Jason Doyle Dorn purchased and
3 ingested the following TDF Drug for an FDA-approved use of the drug: Atripla beginning in 2008. As
4 a result of Gilead's wrongful conduct with respect to the defective TDF Drug, Plaintiff ingested and
5 was injured by the foregoing TDF Drug. Plaintiff's ingestion of the TDF Drug caused and/or
6 contributed to Plaintiff suffering bone demineralization, which resulted in a diagnosis of osteoporosis
7 and multiple bone fractures. Plaintiff required and incurred and will continue to require and incur
8 expenses in connection with medical treatment as a result of these injuries, including surgery. Plaintiff
9 has endured and will continue to endure pain, suffering, mental anguish, and loss of enjoyment of life
10 as a result of his injuries, has suffered lost earnings and/or a loss of earning capacity, and other injuries
11 and damages to be proven at trial.
12

13 28. Plaintiff John Doe 14 is and was at all relevant times a citizen of the State of Georgia
14 and domiciled in Stone Mountain, Georgia. Plaintiff John Doe 14 purchased and ingested the following
15 TDF Drug for an FDA-approved use of the drug: Complera beginning in 2012. As a result of Gilead's
16 wrongful conduct with respect to the defective TDF Drug, Plaintiff ingested and was injured by the
17 foregoing TDF Drug. Plaintiff's ingestion of the TDF Drug caused and/or contributed to Plaintiff
18 suffering bone demineralization, which resulted in a diagnosis of osteopenia. Plaintiff required and
19 incurred and will continue to require and incur expenses in connection with medical treatment as a
20 result of these injuries. Plaintiff has endured and will continue to endure pain, suffering, mental
21 anguish, and loss of enjoyment of life as a result of his injuries, has suffered lost earnings and/or a loss
22 of earning capacity, and other injuries and damages to be proven at trial.
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24 29. Plaintiff Linda Coleman is and was at all relevant times a citizen of the Commonwealth
25 of Pennsylvania and domiciled in Upper Darby, Pennsylvania. Plaintiff Linda Coleman purchased and
26 ingested the following TDF Drug for an FDA-approved use of the drug: Truvada beginning in 2012.
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1 As a result of Gilead's wrongful conduct with respect to the defective TDF Drug, Plaintiff ingested
2 and was injured by the foregoing TDF Drug. Plaintiff's ingestion of the TDF Drug caused and/or
3 contributed to Plaintiff suffering bone demineralization, which resulted in a diagnosis of osteopenia.
4 Plaintiff Linda Coleman required and incurred and will continue to require and incur expenses in
5 connection with medical treatment as a result of these injuries. Plaintiff has endured and will continue
6 to endure pain, suffering, mental anguish, and loss of enjoyment of life as a result of her injuries, has
7 suffered lost earnings and/or a loss of earning capacity, and other injuries and damages to be proven
8 at trial.
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10 30. Plaintiff Marquis D. Green is and was at all relevant times a citizen of the State of
11 California and domiciled in Stockton, California. Plaintiff Marquis D. Green purchased and ingested
12 the following TDF Drug for an FDA-approved use of the drug: Truvada beginning in 2011. As a result
13 of Gilead's wrongful conduct with respect to the defective TDF Drug, Plaintiff ingested and was
14 injured by the foregoing TDF Drug. Plaintiff's ingestion of the TDF Drug caused and/or contributed
15 to Plaintiff suffering kidney failure requiring dialysis treatments. Plaintiff required and incurred and
16 will continue to require and incur expenses in connection with medical treatment as a result of these
17 injuries. Plaintiff has endured and will continue to endure pain, suffering, mental anguish, and loss of
18 enjoyment of life as a result of his injuries, has suffered lost earnings and/or a loss of earning capacity,
19 and other injuries and damages to be proven at trial.
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22 31. Plaintiff Melissa A. Webb is and was at all relevant times a citizen of the State of
23 Alabama and domiciled in Tuscaloosa, Alabama. Plaintiff Melissa A. Webb purchased and ingested
24 the following TDF Drug for an FDA-approved use of the drug: Truvada beginning in 2006. As a result
25 of Gilead's wrongful conduct with respect to the defective TDF Drug, Plaintiff ingested and was
26 injured by the foregoing TDF Drug. Plaintiff's ingestion of the TDF Drug caused and/or contributed
27 to Plaintiff suffering kidney failure. Plaintiff required and incurred and will continue to require and
28

1 incur expenses in connection with medical treatment as a result of these injuries. Plaintiff has endured
2 and will continue to endure pain, suffering, mental anguish, and loss of enjoyment of life as a result of
3 her injuries, has suffered lost earnings and/or a loss of earning capacity, and other injuries and damages
4 to be proven at trial.

5
6 32. Plaintiff Sheila W. Beard is and was at all relevant times a citizen of the State of
7 Alabama and domiciled in Tuscaloosa, Alabama. Plaintiff Sheila W. Beard purchased and ingested the
8 following TDF Drugs for an FDA-approved use of the drugs: Atripla and Truvada beginning in 2008.
9 As a result of Gilead's wrongful conduct with respect to the defective TDF Drugs, Plaintiff ingested
10 and was injured by the foregoing TDF Drugs. Plaintiff's ingestion of the TDF Drugs caused and/or
11 contributed to Plaintiff suffering kidney failure. Plaintiff required and incurred and will continue to
12 require and incur expenses in connection with medical treatment as a result of these injuries. Plaintiff
13 has endured and will continue to endure pain, suffering, mental anguish, and loss of enjoyment of life
14 as a result of her injuries, has suffered lost earnings and/or a loss of earning capacity, and other injuries
15 and damages to be proven at trial.

16
17 33. Plaintiff Stephen Joiner is and was at all relevant times a citizen of the State of Georgia
18 and domiciled in Lithonia, Georgia. Plaintiff Stephen Joiner purchased and ingested the following TDF
19 Drugs for an FDA-approved use of the drugs: Truvada, Atripla and Stribild beginning in 2004. As a
20 result of Gilead's wrongful conduct with respect to the defective TDF Drugs, Plaintiff ingested and
21 was injured by the foregoing TDF Drugs. Plaintiff's ingestion of the TDF Drugs caused and/or
22 contributed to Plaintiff suffering bone density loss, which resulted in a diagnosis of osteoporosis and
23 a fracture to Plaintiff's foot. Plaintiff required and incurred and will continue to require and incur
24 expenses in connection with medical treatment as a result of these injuries. Plaintiff has endured and
25 will continue to endure pain, suffering, mental anguish, and loss of enjoyment of life as a result of his
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1 injuries, has suffered lost earnings and/or a loss of earning capacity, and other injuries and damages to
2 be proven at trial.

3 34. Defendant Gilead Sciences, Inc. is a Delaware corporation with its principle place of
4 business at 333 Lakeside Drive, Foster City, California. Gilead is a biopharmaceutical company that
5 develops, manufactures, markets, and sells prescription medicine, including, but not limited to, Viread,
6 Truvada, Atripla, Complera, Stribild, Genvoya, Odefsey, and Descovy. Gilead reported revenue of
7 \$26.1 billion dollars in 2017 and has operations worldwide.

8 V. FACTUAL ALLEGATIONS

9 35. Gilead's "Company Overview" states: "With each new discovery and investigational
10 new drug candidate, we seek to improve the care of patients living with life-threatening diseases around
11 the world."³ It would more accurately state: We seek to improve the care of patients living with life-
12 threatening diseases *only if and when it suits the company's financial needs*.

13 A. Background

14 1. Laws and regulations governing the approval and labeling of prescription drugs.

15 36. The Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") requires
16 manufacturers that develop a new drug product to file a New Drug Application ("NDA") in order to
17 obtain approval from the Food and Drug Administration ("FDA") before selling the drug in interstate
18 commerce. 21 U.S.C. § 355.

19 37. The NDA must include, among other things, data regarding the safety and effectiveness
20 of the drug, information on any patents that purportedly cover the drug or a method of using the drug,
21 and the labeling proposed to be used for the drug. 21 U.S.C. § 355(b).

22 38. Manufacturers with an approved NDA must review all adverse drug experience
23 information obtained by or otherwise received by them from any source, including but not limited to
24 postmarketing experience, reports in the scientific literature, and unpublished scientific papers. 21
25 C.F.R. § 314.80(b).

26
27 ³ See, e.g., Gilead Sciences Company Overview, available at <http://www.gilead.com/~media/Files/pdfs/other/US%20Corporate%20Overview%20%20111014.pdf>.

1 39. After FDA approval, manufacturers may only promote drugs in a manner consistent
2 with the contents of the drug’s FDA-approved label. 21 C.F.R. § 202.1. The FDA’s Division of Drug
3 Marketing, Advertising, and Communications monitors manufacturers’ promotional activities and
4 enforces the FDCA and its implementing regulations to ensure compliance.

5 40. Under what is known as the Changes Being Effectuated (“CBE”) regulation, a
6 manufacturer with an approved NDA can make certain changes to its label without prior FDA approval
7 by simply sending the FDA a “supplemental submission.” 21 C.F.R. § 314.70(c)(6)(iii).

8 41. Changes to the labeling a manufacturer can make pursuant to CBE without prior FDA
9 approval include those to “add or strengthen a contraindication, warning, precaution, or adverse
10 reactions for which the evidence of causal association satisfies the standard for inclusion in the labeling
11 under § 201.57(c) of this chapter” and “to add or strengthen an instruction about dosage and
12 administration that is intended to increase the safe use of the drug product.” 21 C.F.R.
13 § 314.70(c)(6)(iii)(A) and (C).

14 42. A manufacturer must revise its label “to include a warning about a clinically significant
15 hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship
16 need not have been definitively established.” 21 C.F.R. § 201.57(c)(6).

17 43. The warnings section of the label “must identify any laboratory tests helpful in
18 following the patient’s response or in identifying possible adverse reactions. If appropriate,
19 information must be provided on such factors as the range of normal and abnormal values expected in
20 the particular situation and the recommended frequency with which tests should be performed before,
21 during, and after therapy.” *Id.* § 201.57(c)(6)(iii). According to an FDA Guidance for Industry on the
22 warnings and precautions section of the labeling, “[i]nformation about the frequency of testing and
23 expected ranges of normal and abnormal values should also be provided if available.”⁴

24 44. Adverse reactions must be added to the label where there “is some basis to believe there
25 is a causal relationship between the drug and the occurrence of the adverse event.” *Id.* § 201.57(c)(7).

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⁴ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>.

1 45. An August 22, 2008 amendment to these regulations provides that a CBE supplement
2 to amend the labeling for an approved product must reflect “newly acquired information.” 73 Fed.
3 Reg. 49,609. “Newly acquired information” is not limited to new data but also includes “new analysis
4 of previously submitted data.” “[I]f a sponsor submits adverse event information to FDA, and then
5 later conducts a new analysis of data showing risks of a different type or of greater severity or
6 frequency than did reports previously submitted to FDA, the sponsor meets the requirement for ‘newly
7 acquired information.’” *Id.* at 49,607.

8 46. Under the 1984 Hatch-Waxman Amendments to the Act, Congress sought to expedite
9 the entry of less expensive generic versions of brand name drugs by simplifying the generic approval
10 process. A generic manufacturer seeking to sell a generic version of a brand name drug may file an
11 Abbreviated New Drug Application (“ANDA”), which relies on the brand manufacturer’s safety and
12 efficacy data. The ANDA filer must demonstrate that its proposed generic product is therapeutically
13 equivalent to the brand name drug, meaning that it: (a) contains the same active ingredient(s), dosage
14 form, route of administration, and strength as the brand name drug; and (b) is bioequivalent to the
15 brand drug (i.e., the drugs exhibit the same rate and extent of absorption).

16 47. As a counter-balance to the abbreviated process for the approval of generic drugs,
17 Hatch-Waxman may grant brand manufacturers a period of market exclusivity upon approval of the
18 NDA. For example, Hatch-Waxman grants a five-year period of exclusivity (regardless of any patent
19 protection) to products containing chemical entities not previously approved by the FDA. Under this
20 five-year exclusivity, the FDA cannot even accept an ANDA to make a generic version of the drug for
21 four or five years from NDA approval (depending upon whether the generic asserted that the brand’s
22 patents were invalid or not infringed).

23 48. Hatch-Waxman also streamlined the process for brand manufacturers to attempt to
24 enforce their patents against potential infringement by generic manufacturers. If an ANDA contains a
25 certification that the patents the brand has listed in its NDA are invalid or will not be infringed by the
26 ANDA generic product (a “Paragraph IV certification”), the brand manufacturer can automatically
27 delay FDA approval of the generic drug by suing the generic manufacturer for patent infringement. If
28 the brand manufacturer brings a patent infringement action against the generic filer within 45 days of

1 receiving notification of the Paragraph IV certification, the FDA may not grant final approval to the
2 ANDA until the earlier of (a) the passage of two and a half years, or (b) the issuance of a court decision
3 that the patent is invalid or not infringed by the generic manufacturer's ANDA. 21 U.S.C.
4 § 355(j)(5)(B)(iii).

5 49. Generic drugs that are therapeutically equivalent to the brand name drug may be
6 automatically substituted for the brand at the pharmacy counter. Due to state automatic substitution
7 laws that permit or require generic substitution, once a generic version of a brand-name drug enters
8 the market, the generic quickly captures the vast majority of the brand's sales, often obtaining 80% or
9 more of unit sales within the first six months. On average, generics capture 90% of brand unit sales
10 within the first year of generic entry.

11 **2. Tenofovir and Gilead's TDF- and TAF- containing drug products indicated for**
12 **use in treating HIV.**

13 50. Tenofovir (chemical name, 9-(2-Phosphonomethoxypropyl)adenine ("PMPA")) is a
14 type of medicine called a nucleotide analog reverse transcriptase and HBV polymerase inhibitor
15 ("NRTI").

16 51. In order for HIV to infect a healthy human cell, the virus must convert its ribonucleic
17 acid ("RNA") based genome into a strand of complementary deoxyribonucleic acid ("DNA"). This
18 process of converting the virus's RNA into DNA is reverse transcription, and is performed by an
19 enzyme named reverse transcriptase. Reverse transcription occurs inside the human cell that the virus
20 is infecting.

21 52. NRTIs prevent the reverse transcriptase from converting its RNA into DNA, preventing
22 the infection of the cell and spread of HIV. In order for NRTIs to stop HIV from infecting a cell, the
23 drug must be absorbed into the cell and "activated" by the cell's biological machinery. The "activated"
24 form of tenofovir is known as tenofovir-diphosphate ("TFV-DP").

25 53. When used to treat HIV infection, tenofovir must be administered in combination with
26 other anti-HIV drugs, a practice known as "combination antiretroviral therapy" or "cART." By using
27 a combination of different classes of medications, physicians can customize treatment based on factors
28 including how much virus is in the patient's blood, the particular strain of the virus, and disease

1 symptoms. The aim of cART is to reduce the viral load—i.e., the amount of virus per unit of blood or
2 plasma, of patients to levels where commercial viral load tests cannot detect the presence of the virus
3 (generally a concentration of lower than 50 HIV-1 RNA copies per mL of plasma). A cART treatment
4 regimen can incorporate multiple standalone pills or a single pill coformulated with all drugs necessary
5 for the regimen.

6 54. Gilead did not discover tenofovir. Tenofovir was discovered in the mid-1980s by the
7 collaborative research efforts of scientists in Prague and Belgium. Although the anti-HIV properties
8 of tenofovir were promising, it had a significant downside. When tenofovir is administered by mouth,
9 very little of it is absorbed into the body.

10 55. Because an intravenous formulation had little sales potential, Gilead developed a
11 prodrug form of tenofovir that can be taken orally. Prodrugs are pharmacologically inactive
12 compounds that can be more efficiently absorbed into the bloodstream and then converted into the
13 active form of the drug within the body.

14 56. One prodrug of tenofovir is tenofovir disoproxil (chemical name,
15 bis(isopropylloxycarbonyloxymethyl)-PMPA or bis-POC PMPA). The fumaric salt of tenofovir
16 disoproxil is tenofovir disoproxil fumarate, commonly known as TDF.

17 57. While TDF is able to be taken by mouth, the proportion of tenofovir that enters the cells
18 is relatively low. In order to have the desired therapeutic effect, a high dose of TDF must be
19 administered. The standard dose of TDF for HIV treatment and prevention in adults is relatively
20 large—300 mg taken once a day. A general principle of toxicology is that the “dose makes the
21 poison”—i.e., larger doses are generally associated with higher rates of toxicity and adverse events.
22 Tenofovir is no different.

23 58. Gilead has received FDA approval for five TDF-based drugs for the treatment of HIV.

24 59. On October 26, 2001, the FDA approved Gilead’s NDA 21356 for Viread (300 mg
25 TDF) tablets for use in combination with other antiretroviral agents for the treatment of HIV-1
26 infection. Gilead submitted limited clinical data supporting approval of the drug. Gilead had not
27 completed Phase III clinical studies. Gilead excluded from its clinical trials people who had serious
28 preexisting kidney dysfunction. And Gilead only studied Viread in treatment-experienced patients

1 (those who had previously been treated for HIV). In 2008, the FDA approved an additional Viread
2 indication for the treatment of Chronic Hepatitis B.

3 60. On August 2, 2004, the FDA approved Gilead's NDA 21752 for Truvada tablets, which
4 is a combination product containing 300 mg TDF (i.e., Viread) and 200 mg emtricitabine, for use in
5 combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. Neither of
6 the active ingredients in Truvada was new. The FDA approved the Truvada application based primarily
7 on data showing the fixed-dose combination drug was bioequivalent to its separate components. On
8 July 16, 2012, the FDA approved an additional indication for the use of Truvada in combination with
9 safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1
10 in adults at high risk.

11 61. On July 12, 2006, the FDA approved Gilead's NDA 21937 for Atripla tablets, which is
12 a combination product containing 300 mg TDF, 200 mg emtricitabine, and 600 mg efavirenz, for use
13 alone as a complete regimen or in combination with other retroviral agents for the treatment of HIV-1
14 infection in adults. Gilead submitted no clinical data in support of NDA 21937. None of the active
15 ingredients in Atripla were new. Approval was based on a demonstration of bioequivalence between
16 the individual components and the fixed-dose combination.

17 62. On August 10, 2011, the FDA approved Gilead's NDA 202123 for Complera tablets,
18 which is a fixed dose combination product containing 300 mg TDF, 200 mg emtricitabine, and 25 mg
19 rilpivirine, for use as a complete regimen for the treatment of HIV-1 infection in treatment-naïve adults
20 (i.e., adults who had not been previously treated for HIV). None of the active ingredients in Complera
21 were new. Gilead submitted no new clinical safety or efficacy trials in connection with NDA 20123.
22 Approval was based on the results of bioequivalence studies comparing the combination product to
23 the individual component drugs. In addition, the primary focus of the FDA's safety and medical review
24 of the Complera NDA was on rilpivirine, since that drug was the most recently approved component
25 of the fixed dose combination Complera tablet.

26 63. On August 27, 2012, the FDA approved Gilead's NDA 203100 for Stribild, which is a
27 fixed dose combination product containing 300 mg TDF, 200 mg emtricitabine, 150 mg elvitegravir,
28 and 150 mg cobicistat, for use as a complete regimen for the treatment of HIV-1 infection in treatment-

1 naïve adults. Although elvitegravir and cobicistat had not been previously approved by the FDA, the
2 FDA gave Gilead’s Stribild NDA a 10-month standard review because there were already multiple
3 regimens available for treatment naïve patients including one pill, once-a-day regimens.

4 64. Before the FDA approved Viread in 2001, Gilead had discovered another prodrug
5 version of tenofovir, which it originally called GS-7340 and which is now known as tenofovir
6 alafenamide fumarate (“TAF”). TDF and TAF are two prodrug versions of the same parent drug,
7 tenofovir, though TAF requires a dose more than ten times smaller than TDF to achieve the same
8 therapeutic effect.

9 65. TAF differs from TDF in its penetration into target cells. Unlike TDF, which is
10 converted into the parent drug tenofovir in the gastrointestinal tract, liver, and blood, TAF is not
11 converted into tenofovir until it has been absorbed by the cell. This allows TAF to be more efficiently
12 absorbed by “target cells”—i.e., cells that HIV infects or “targets”—compared to TDF. This more
13 efficient absorption allows TAF to achieve far greater intracellular concentrations of the activated drug
14 (tenofovir-diphosphate) in target cells than even a dramatically larger dose of TDF. This enhanced
15 efficiency in absorption leads to plasma concentrations of tenofovir that are 90% lower than TDF,
16 while still maintaining intracellular concentrations of activated drug in target cells that is the same or
17 higher than TDF. The lowered plasma concentrations of tenofovir found with TAF result in reduced
18 toxicity compared to TDF, making TAF safer to use than TDF.

19 66. On November 5, 2015, the FDA approved Gilead’s first TAF-based design—NDA
20 207561 for Genvoya tablets, a fixed dose combination product which contains 10 mg TAF, 200 mg
21 emtricitabine, 150 mg elvitegravir, and 150 mg cobicistat. Genvoya is indicated for the treatment of
22 HIV-1 infection in adults and pediatric patients 12 years of age or older who have no antiretroviral
23 treatment history or to replace the current antiretroviral regimen in those who are virologically
24 suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least six
25 months with no history of treatment failure and no known substitutions associated with resistance to
26 the individual components of Genvoya. The TDF-based counterpart to Genvoya is Stribild. Genvoya
27 is identical to Stribild except for the substitution of TAF for TDF.

1 67. On March 1, 2016, the FDA approved Gilead's NDA 208351 for Odefsey tablets, which
2 is a combination product containing 25 mg TAF, 200 mg emtricitabine, and 25 mg rilpivirine, for use
3 as a complete regimen for the treatment of HIV-1 infection in patients 12 years of age and older as
4 initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than or equal to
5 100,000 copies per mL; or to replace a stable antiretroviral regimen in those who are virologically-
6 suppressed (HIV-1 RNA less than 50 copies per mL of blood or plasma) for at least six months with
7 no history of treatment failure and no known substitutions associated with resistance to the individual
8 components of Odefsey. The TDF-based counterpart to Odefsey is Complera. Odefsey is identical to
9 Complera except for the substitution of TAF for TDF.

10 68. On April 4, 2016, the FDA approved Gilead's NDA 208215 for Descovy tablets, which
11 is a fixed dose combination product containing 25 mg TAF and 200 mg emtricitabine, for use in
12 combination with other antiretroviral agents, for treatment of HIV-1 infection in adults and pediatric
13 patients 12 years of age or older. The TDF-based counterpart to Descovy is Truvada. Descovy is
14 identical to Truvada except for the substitution of TAF for TDF. On October 3, 2019, the FDA
15 approved an additional indication of Descovy for use in PrEP.

16 69. Upon information and belief, Gilead has not sought FDA approval of a standalone TAF
17 drug product for the treatment of HIV. Viread, therefore, has no TAF-based counterpart for the
18 treatment of HIV infection. Although the FDA approved Gilead's NDA 208464 for Vemlidy (300 mg
19 TAF) tablets on November 10, 2016, Gilead only sought approval to market Vemlidy for the treatment
20 of Hepatitis B infection in adults with compensated liver disease and thus cannot be marketed for the
21 treatment of HIV.

22 **B. Gilead knew before Viread was approved that TDF posed a significant safety risk.**

23 70. Before Gilead's first TDF product, Viread, received FDA approval in 2001, Gilead
24 knew that two of its other antiviral drugs that are structurally similar to tenofovir caused significant
25 kidney damage.

1 71. Tenofovir is a member of a class of molecules known as “acyclic nucleoside
2 phosphonates.” Two of Gilead’s other antiviral drugs—cidofovir and adefovir⁵—are also acyclic
3 nucleoside phosphonates.

4 72. Cidofovir injection, marketed as Vistide, was Gilead’s first commercial product. When
5 the FDA approved Vistide in 1996, it carried a black box warning stating that renal impairment is the
6 drug’s major toxicity and renal failure resulting in dialysis or contributing to death have occurred with
7 as few as one or two doses of Vistide.

8 73. In December 1999, Gilead abandoned development of NRTI prodrug adefovir
9 dipivoxil for the treatment of HIV after it proved so toxic to patients’ kidneys in the later stages of
10 Phase III clinical trials. In Gilead’s clinical trial GS-408, 59% of patients demonstrated severe kidney
11 toxicity after 72 weeks. One patient in the trial died due to multiorgan failure subsequent to kidney
12 failure. Based on this experience, Gilead knew that adefovir dipivoxil was associated with delayed
13 nephrotoxicity—meaning that its toxic effects might not be felt for some time after continued use.
14 Gilead would later develop and market adefovir dipivoxil as Hepsera for treatment of hepatitis B virus
15 infection. Critically, Gilead recognized that if it reduced the dose of adefovir dipivoxil from 120 mg—
16 as used in trial GS-408 for the treatment of HIV—to 10 mg (the dose in Hepsera), an effective dose
17 for hepatitis B virus treatment, the risk of nephrotoxicity is dramatically reduced.

18 74. Tenofovir has a nearly identical structure to adefovir, varying only by the presence of
19 a methyl group (i.e., a carbon atom bound to three hydrogen atoms) in tenofovir, which replaces a
20 hydrogen atom in adefovir. As Gilead recognized in its 10-K for the year ending December 31, 2000,
21 due to its experiences with nephrotoxicity in Phase III clinical trials of adefovir dipivoxil, delayed
22 toxicity issues similar to those experienced with adefovir dipivoxil could arise with TDF.

23 75. Gilead also knew that while prodrugs allow the drug to be efficiently absorbed into the
24 bloodstream and then converted into an active form within the body, the conversion of the TDF
25
26

27 ⁵ Like tenofovir, only a prodrug of adefovir—adefovir dipivoxil—can be effectively administered
28 orally.

1 prodrug into free tenofovir outside the cell, and the presence of high levels of free tenofovir in the
2 blood, endangers the kidneys.

3 76. The primary purpose of the kidney is to filter out toxins and waste products from the
4 blood, as well as help maintain the delicate balance of water, salts and other compounds in a person's
5 blood. The functional unit of the kidney is the nephron, a microscopic structure that consists of two
6 primary components: a renal "corpuscle" and a renal "tubule." On average, each kidney contains
7 hundreds of thousands to millions of nephrons.

8 77. The renal corpuscle is the component of the nephron that directly filters the blood.
9 Blood flows through a network of capillaries (small blood vessels) known as the glomerulus. The walls
10 of these capillaries work as a filter, allowing certain compounds, as well as water, to pass through. The
11 fluid that is filtered through the capillary walls in the glomerulus, known as the filtrate, is collected by
12 a structure known as Bowman's capsule. One of the ways kidney function is measured is by the rate
13 of blood that is filtered by the glomeruli. This is known as the glomerular filtration rate or "GFR."⁶

14 78. In Bowman's capsule, the filtrate is collected and drains into the other primary
15 component of the nephron, the tubule. Glomerular filtration is highly effective at removing many
16 toxins, but it also filters out many compounds, like water and electrolytes, that a person needs. In the
17 tubule, the cells lining the tubule put these crucial, non-toxic compounds back into the blood, as well
18 as filter out remaining toxins that glomerular filtration did not remove. After the filtrate exits the tubule,
19 it drains into the bladder. This processed filtrate is urine.

20 79. This system of filtering the blood is extremely important and delicate. TDF primarily
21 damages the nephron tubule, due to hyper-concentration of free tenofovir within the tubule cells of the
22

23 ⁶ GFR is not measured directly. Physicians typically estimate a patient's GFR by testing for serum
24 creatinine or by calculating creatinine clearance. Creatinine is a waste product that is produced by the
25 breakdown of muscle tissue and created at a relatively constant rate by the body. The kidneys filter
26 creatinine from the blood into the urine, and reabsorb almost none of it. If the kidney is damaged, the
27 ability of the body to remove creatinine from the blood can be reduced, resulting in high levels of
28 creatinine in the blood. Serum creatinine is the amount of creatinine in the blood. Creatinine clearance
is the rate at which the kidneys clear creatinine from the blood and is measured using the amount of
creatinine present in urine over 24 hours. As renal function goes down, creatinine clearance also goes
down.

1 nephron, which results in cell death or dysfunction. If the tubule cells are dysfunctional or dead, they
2 are unable or less able to perform the vital function of filtering waste and/or toxins and reabsorbing
3 beneficial compounds. Tubular injury can occur without a decline in a patient's glomerular filtration
4 rate. Physicians must monitor other markers of kidney function—those that assess tubule function
5 specifically, like serum phosphorus or urine glucose, to assess a patient's true kidney health.

6 80. Because tenofovir is renally eliminated, through glomerular filtration and proximal
7 tubular secretion, patients are exposed to an increased concentration of tenofovir as the kidneys
8 become damaged. Because exposure to an increased concentration of tenofovir increases toxicity,
9 patients' kidney function must be monitored to ensure that their kidneys remain healthy enough to
10 receive tenofovir.

11 81. Since scientists first synthesized TDF, studies have consistently shown that it could
12 cause significant kidney and bone damage. For example, an animal study published in 1999 showed
13 that high doses of tenofovir were associated with significant bone toxicity in both simian
14 immunodeficiency virus (SIV, the non-human primate version of HIV) infected and uninfected rhesus
15 macaques, with a quarter of the treated animals experiencing significant bone toxicity.

16 82. Gilead's preclinical studies of TDF showed that it could be toxic to kidneys and bones.
17 Preclinical animal studies of TDF showed evidence of renal toxicity and that TDF exposure caused
18 bone toxicity in the form of softening of the bones (osteomalacia) and reduced bone mineral density.
19 Nephrotoxicity in animal models was related to dose as well as to duration of therapy.

20 83. Gilead also knew that the relatively high dose of TDF needed to achieve the desired
21 therapeutic effect created a greater risk of toxic effects, and that bone and kidney toxicities were even
22 more likely with the long-term use of TDF which was needed to combat a disease with no known cure.

23 **C. Gilead's knowledge of TDF toxicity grew as patients' kidneys and bones were**
24 **damaged by the TDF Drugs.**

25 84. As soon as Gilead began marketing Viread, patients started experiencing the
26 nephrotoxic effects of TDF.

27 85. In November 2001, less than one month after Viread entered the market, the first
28 published case of TDF-associated acute renal failure occurred. Thereafter, additional reports of TDF-

1 associated kidney damage, including but not limited to Fanconi syndrome, renal failure, renal tubular
2 dysfunction, and nephrogenic diabetes insipidus, began to appear in the medical literature. Many of
3 those adverse events occurred in patients without preexisting kidney dysfunction.

4 86. Gilead was also seeing renal adverse events in its postmarketing safety data. In fact, the
5 most common serious adverse events reported to Gilead were renal events, including renal failure,⁷
6 Fanconi syndrome,⁸ and serum creatinine increase.

7 87. In the first two years Viread was on the market, 40% of Viread adverse events reports
8 received by Gilead were related to the renal/urinary system. This included 49 cases of increased
9 creatinine, 16 cases of hypophosphatemia,⁹ 42 cases of renal insufficiency, 51 cases of acute renal
10 failure, 6 cases of chronic renal failure, and 32 cases of Fanconi syndrome. These numbers are far less
11 than the true incidence of kidney damage experienced by Viread patients during this timeframe because
12 postmarketing adverse events are underreported.

13 88. Gilead had to update its Viread labeling at least four times to describe the kidney
14 damage patients experienced when taking TDF:

- 15 a. On December 2, 2002, Gilead added that patients had suffered renal
16 impairment, including increased creatinine, renal insufficiency, kidney failure,
17 and Fanconi syndrome, with Viread use;
- 18 b. On October 14, 2003, Gilead added more kidney disorders, including acute
19 renal failure, proximal tubulopathy,¹⁰ and acute tubular necrosis;¹¹

21 ⁷ When the kidney cannot filter the blood normally, a patient is usually diagnosed with “renal
22 failure.”

23 ⁸ If damage to the tubule prevents the reabsorption of beneficial molecules from filtrate, the levels
24 of these beneficial compounds can become dangerously low in the blood. This is known as Fanconi
25 syndrome.

26 ⁹ Hypophosphatemia is a low level of phosphorus in the blood, which can indicate that the ability
27 of the nephron tubule to reabsorb phosphorus from the filtrate is damaged.

28 ¹⁰ Proximal tubulopathy refers to damage or dysfunction to the portion of the nephron tubule that
is closest to Bowman’s capsule.

¹¹ Acute tubular necrosis refers to the death of the cells that line the nephron tubule. This is
associated with loss of kidney function.

- c. On May 12, 2005, Gilead added nephrogenic diabetes insipidus;¹² and
- d. On March 8, 2006, Gilead added polyuria¹³ and nephritis¹⁴ to the list of renal and urinary disorders that patients had experienced while on TDF.

As Gilead knew, injuries were not limited to patients with a history of renal dysfunction or other risk factors.

89. Gilead's long-term clinical data also demonstrated that TDF was damaging patients' bones. 48-week data showed greater decreases from baseline in bone mineral density at the lumbar spine and hip in patients taking Viread compared to those receiving other HIV drugs. At 144 weeks, there was a significantly greater decrease from baseline in bone mineral density at the lumbar spine in patients taking Viread compared to those receiving other HIV drugs, as well as significant increases in biochemical markers of bone turnover in patients taking Viread. And once Gilead began conducting clinical trials with Viread in adolescent and pediatric patients, the effects of TDF on adolescent and pediatric patients' bones were similar to the effects seen with adult patients.

90. After Gilead brought Truvada to market, the medical literature continued to identify cases of TDF-associated kidney damage, including in patients without preexisting renal dysfunction or co-administration with another nephrotoxic drug.

91. Several new studies presented at the February 2006 Conference on Retroviruses and Opportunistic Infections ("CROI") highlighted the frequency of nephrotoxicity in TDF-treated patients. In one study, CDC investigators analyzed longitudinal data from 11,362 HIV-infected patients, all of whom had GFR > 90mL/min at baseline, and found that treatment with TDF was significantly associated with mild and moderate renal insufficiency. In another, observational study of 497 patients initiating TDF treatment, 17.5% developed renal dysfunction. The most severe declines in renal function were associated with TDF treatment as part of a boosted regimen.

¹² Nephrogenic diabetes insipidus refers to a condition characterized by the production of a large amount of dilute urine as a result of kidney dysfunction. It is thought to be related to damage to the nephron tubule.

¹³ Polyuria refers to the excessive production of urine.

¹⁴ Nephritis refers to the inflammation of the kidneys.

1 92. In 2007, Gilead scientists published an article discussing the company’s knowledge of
2 TDF safety issues over the first four years of TDF treatment. Gilead reported that 0.5% of patients
3 enrolled in a global expanded access program experienced a serious renal adverse event, including
4 acute and chronic renal failure and Fanconi syndrome. A “serious” adverse event meant one resulting
5 in hospitalization or prolongation of hospitalization, death, disability, or requiring medical intervention
6 to prevent permanent impairment. Gilead also reported that through April 2005 the most common
7 serious adverse events reported to Gilead’s postmarketing safety database were renal events, including
8 renal failure, Fanconi syndrome, and serum creatinine increase.

9 93. Although this Gilead article demonstrates the company’s clear and early knowledge of
10 serious TDF toxicity in a significant number of patients, it downplayed the incidence of TDF-
11 associated renal toxicity. In its Medical Review of the Stribild NDA in 2012, the FDA noted the
12 limitations of Gilead’s data, including the short duration of treatment, the voluntary nature of adverse
13 event reporting in some countries, and the fact that Gilead only assessed serious adverse events, and
14 not renal events leading to drug discontinuation or non-serious renal adverse events. According to the
15 FDA, any of these factors may have led to an underestimation of the true incidence of renal events of
16 interest. The FDA similarly questioned Gilead’s data on the incidence of renal adverse events based
17 on its postmarketing safety database given the voluntary nature of reporting.

18 94. Moreover, even if Gilead’s data accurately captured the percentage of patients
19 experiencing serious renal adverse events (which it did not), it would still represent a very large number
20 of patients who experienced significant health problems due to TDF toxicity. For example, in late
21 2015, according to data from Symphony Health Solutions, nearly 500,000 people in the U.S. were
22 ingesting TDF daily. Using Gilead’s numbers, approximately 2,500 of those patients would likely
23 experience severe kidney damage. Now that TDF has been on the market for nearly two decades, many
24 thousands of patients have likely experienced severe TDF-induced kidney damage.

25 95. In May 2007, Gilead had to update its labeling to recognize that TDF-associated renal
26 damage also caused osteomalacia (softening of the bones) in patients. In November 2008, Gilead
27 modified the labeling to state that patients taking TDF had experienced osteomalacia due to proximal
28 renal tubulopathy as bone pain, and that it might contribute to fractures.

1 96. In August 2008, Gilead had to update its labeling to recognize finally that TDF caused
2 both “new onset” and “worsening” renal impairment—meaning, as Gilead knew years prior, that TDF
3 was injuring patients’ kidneys even though they had no preexisting renal dysfunction.

4 97. During 2009–2011, studies continued to show that TDF caused a significant loss of
5 renal function in HIV-infected patients.

6 98. Multiple articles described how the incidence of TDF-induced nephrotoxicity was
7 underreported because studies often excluded patients who were most likely to exhibit nephrotoxic
8 effects, including patients who combined TDF in a ritonavir-boosted regimen or with another
9 nephrotoxic drug, older patients or those with advanced HIV disease, or those with mild baseline renal
10 dysfunction. Notwithstanding selection bias that tended to hide TDF-associated kidney dysfunction,
11 the evidence was clear that TDF caused renal tubular dysfunction in a significant percentage of HIV-
12 infected patients.

13 99. In April 2012, researchers at the San Francisco Veterans’ Administration Medical
14 Center and the University of California, San Francisco published their analysis of the medical records
15 of more than 10,000 HIV-positive veterans in the national VA healthcare system, which is the largest
16 provider of HIV care in the United States. The study authors found that for each year of tenofovir
17 exposure, risk of protein in urine—a marker of kidney damage—rose 34%, risk of rapid decline in
18 kidney function rose 11%, and risk of developing chronic kidney disease rose 33%. The risks remained
19 after the researchers controlled for other kidney disease risk factors such as age, race, diabetes,
20 hypertension, smoking, and HIV-related factors.

21 100. By the time it reviewed the Stribild NDA, the FDA stated that the safety profile of TDF
22 was, by that point, “well-characterized in multiple previous clinical trials and is notable for TDF-
23 associated renal toxicity related to proximal renal tubule dysfunction and bone toxicity related to loss
24 of bone mineral density and evidence of increased bone turnover.”¹⁵

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28 ¹⁵ FDA Center for Drug Evaluation and Research Summary Review for NDA 203100 at 10,
available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203100Orig1s000SumR.pdf.

1 101. With each passing year and each successive TDF product, Gilead learned even more
2 about TDF’s toxicity. Despite this knowledge, Gilead repeatedly designed the TDF Drugs to contain
3 TDF as the tenofovir delivery mechanism rather than safer TAF.

4 **D. Before Gilead developed Stribild, it knew that renal adverse events were more likely**
5 **when patients took TDF as part of a boosted regimen.**

6 102. Before Gilead first started marketing Viread, it knew that patients’ exposure to
7 tenofovir increases significantly when tenofovir is co-administered with a ritonavir-boosted protease
8 inhibitor: the maximum concentration of tenofovir increased 31%; the minimum concentration of
9 tenofovir increased 29%; and the area under the curve (the actual body exposure to the drug after dose
10 administration) increased 34%.

11 103. In the first few years TDF was on the market, many reported cases of tenofovir-related
12 renal damage involved patients taking TDF with a ritonavir-boosted protease inhibitor—leading
13 authors to conclude that the risk of TDF-associated renal toxicity increased for patients on a boosted
14 regimen. This is consistent with other patient populations at increased risk for renal toxicity, including
15 those with low body weight and those taking another nephrotoxic drug; each is associated with higher
16 levels of tenofovir exposure.

17 104. As Gilead recognized in the Precautions section of the July 1, 2004 Viread label:
18 “[h]igher tenofovir concentrations could potentiate Viread-associated adverse events, including renal
19 disorders.”¹⁶

20 105. Gilead further stated: “Atazanavir [another protease inhibitor] and lopinavir/ritonavir
21 have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown.
22 Patients receiving atazanavir and lopinavir/ritonavir and Viread should be closely monitored for
23 Viread-associated adverse events. Viread should be discontinued in patients who develop Viread-
24 associated adverse events.”¹⁷

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26
27 ¹⁶ Viread (tenofovir disoproxil fumarate) Tablets label at 17, available at
https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21356slr010_viread_lbl.pdf.

28 ¹⁷ *Id.*

1 106. Case study authors similarly called for careful monitoring of patients taking TDF in a
2 boosted regimen, given the frequency of renal damage in such patients.

3 107. A 2008 Journal of Infectious Diseases article reported that the odds of developing
4 significant renal function reduction were 3.7 times higher for patients receiving a regimen containing
5 tenofovir plus ritonavir-boosted protease inhibitor than for those receiving tenofovir plus
6 nonnucleoside reverse transcriptase inhibitor-based therapy, even after adjusting for viral load.

7 **E. Before Gilead developed each of the TDF Drugs, it knew that TAF was less toxic to**
8 **kidneys and bones than TDF.**

9 108. Before the FDA approved Viread, Gilead had already discovered a different design for
10 an orally available version of tenofovir that is more potent than TDF, meaning that it can be
11 administered at a significantly lower dose with fewer side effects than TDF.

12 109. Unlike TDF, TAF is not converted into tenofovir until it has been absorbed by the cell.
13 As a result, TAF is more efficiently absorbed by the cells HIV targets compared to TDF. This more
14 efficient absorption allows TAF to achieve far greater intracellular concentrations of the activated drug
15 (tenofovir-diphosphate) in target cells than even a dramatically larger dose of TDF, while achieving
16 plasma concentrations of tenofovir that are 90% lower than TDF. The lowered plasma concentrations
17 of tenofovir found with TAF result in reduced toxicity compared to TDF, making TAF safer to use
18 than TDF.

19 110. On July 21, 2000, Gilead filed a provisional patent application which described TAF
20 (then called GS-7340) as 2–3 times more potent than TDF while providing 10 times the intracellular
21 concentration of tenofovir than TDF. Gilead also demonstrated that dosing with TAF resulted in
22 dramatically higher concentrations of drug in all organs except the kidneys and the liver, compared
23 with TDF. This suggested that TAF is uniquely able to target cells that HIV infects, while not
24 concentrating in the kidney.

25 111. In a 2001 paper, Gilead scientists described the remarkable results achieved when
26 studying the metabolism of TAF in blood. The paper, “Metabolism of GS-7430, A Novel Phenyl
27 Monophosphoramidate Intracellular Prodrug of PMPA, In Blood,” compared the distribution of the
28 active drug tenofovir in blood cells and plasma after exposure to either GS-7430 or tenofovir disoproxil

1 (which was still in clinical development at the time of the study). What Gilead found was that one need
2 only *one thousandth of the dose* of GS-7340 compared to tenofovir to achieve the same level of
3 inhibition of HIV replication in vitro. Gilead also found that one need to use only one tenth the dose
4 of GS-7340 compared to TDF to reach the same levels of active tenofovir inside cells.

5 112. Gilead researchers presented the results of its GS-7340 study at a February 2002
6 Conference on Retroviruses. John Milligan, then Gilead's Vice President of Corporate Development
7 and currently its President and Chief Executive Officer, said that Gilead's goal with GS-7340 was to
8 deliver a more potent version of tenofovir that can be taken in lower doses, resulting in better antiviral
9 activity and fewer side effects. Milligan said that "there's a great need to improve therapy for HIV
10 patients."¹⁸

11 113. Gilead's preclinical studies of TAF also indicated that TAF is less likely to accumulate
12 in renal proximal tubules than TDF, supporting the potential for an improved renal safety profile.

13 114. Gilead's 2001 10-K highlighted the benefits of GS-7340 over Viread: "Both GS 7340
14 and Viread are processed in the body to yield the same active chemical, tenofovir, within cells.
15 However, the chemical composition of GS 7340 may allow it to cross cell membranes more easily than
16 Viread, so that with GS 7340, tenofovir may be present at much higher levels within cells. As a result,
17 GS 7340 may have greater potency than Viread and may inhibit low-level HIV replication in cells that
18 are otherwise difficult to reach with reverse transcriptase inhibitors."¹⁹

19 115. At the end of the first quarter of 2002, Gilead told investors that it had initiated Phase
20 I/II testing of GS-7340. In an earnings call, Gilead stated that it had initiated a dose escalation study
21 for GS-7340 through which Gilead intended to prove that GS-7340 was more potent than Viread,
22 meaning that it could be administered at a safer, lower dose.
23
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25 _____
26 ¹⁸ Special Coverage: 9th Conference on Retroviruses – New drugs, new data hold promise for next
decade of HIV treatment, AIDS Alert, May 1, 2002.

27 ¹⁹ Gilead Sciences, Inc. Form 10-K for the fiscal year ended December 31, 2001, at 13, available
28 at <https://www.sec.gov/Archives/edgar/data/882095/000091205702011690/a2073842z10-k.htm>.

1 116. In an October 28, 2003 earnings call, Gilead told analysts that data from the ongoing
2 Phase I/II study of GS-7340 “look[ed] promising.”²⁰

3 117. In December 2003, Mark Perry, then Gilead’s Executive Vice President of Operations,
4 told investors that Gilead was “excited” about GS-7340. Gilead expected GS-7340 to achieve “more
5 potency at lower doses and increase the therapeutic index for” tenofovir.²¹ The “therapeutic index” is
6 a comparison of the amount of a therapeutic agent that causes the therapeutic effect compared to the
7 amount that causes toxicity.

8 118. In January 2004, Gilead repeatedly referred to the positive results from clinical studies
9 of GS-7340 in calls with analysts and disclosures to the investment industry. On a January 29, 2004
10 earnings call, Gilead stated that, based on these positive results, it was designing a Phase II program
11 for GS-7340 to determine the safety and efficacy of the compound in treatment naïve patients and in
12 highly treatment experienced patients.

13 119. At a May 2004 Deutsche Bank Securities Healthcare Conference, Gilead said that it
14 knew GS-7340 could be dosed at a fraction of the Viread dose and give a greater antiviral response.

15 120. However, on October 21, 2004, shortly after the FDA approved Truvada, Gilead
16 abruptly announced that it would abandon its GS-7340 design. It stated:

17
18 Earlier this year as a result of positive data from a small phase I/II study
19 of GS 7340, we began designing a phase II program to determine the
20 safety and efficacy of the compound in treatment-naïve patients and in
21 highly treatment experienced patients. Since that time we have
22 witnessed the increasing use of Viread across all HIV patient
23 populations, and we have also received approval for and launched
24 Truvada.

25
26 Based on our internal business review and ongoing review of the
27 scientific data for GS 7340, we came to the conclusion that it would be
28 unlikely that GS 7340 would emerge as a product that could be highly
differentiated from Viread.²²

25 ²⁰ Event Brief of Q3 2003 Gilead Sciences Earnings Conference Call – Final, FD (Fair Disclosure)
Wire, Oct. 28, 2003.

26 ²¹ Gilead Sciences at Harris Nesbitt Gerard Healthcare Conference 2003 – Final, FD (Fair
27 Disclosure) Wire, Dec. 11, 2003.

28 ²² <https://www.gilead.com/news/press-releases/2004/10/gilead-discontinues-development-of-gs-9005-and-gs-7340-company-continues-commitment-to-research-efforts-in-hiv>.

1 121. Prior to its October 2004 announcement, Gilead never indicated that there might be an
2 issue with differentiating GS-7340 from Viread or expressed any other negative view of the prospects
3 of GS-7340. To the contrary, Gilead repeatedly touted the positive results of preclinical and clinical
4 studies of GS-7340 and the benefits of GS-7340 over Viread.

5 122. Gilead’s “internal business review” was the real driver of its decision to abandon a
6 design it knew to be safer than Viread.

7 123. In May 2005, despite Gilead’s misrepresentation that GS-7340 was not worth pursuing,
8 Gilead scientists reported the favorable results they achieved with GS-7340, including its benefits over
9 Viread, in an issue of Antimicrobial Agents and Chemotherapy. Reuters Health News covered the
10 article:

11 After oral administration of GS 7340 to dogs, tenofovir concentrations
12 were 5- to 15-fold higher in lymph nodes than after tenofovir DF
13 administration, the researchers note. Except for kidney and liver, tissue
concentrations of tenofovir were generally higher after GS 7340 than
after tenofovir DF administration.

14 “The high concentrations of tenofovir observed in lymphatic tissues
15 after oral administration of GS 7340 are expected to result in increased
16 clinical potency relative to tenofovir DF and could have a profound
effect on the low-level virus replication that occurs in tissues with
suboptimal drug exposure during HAART,” the authors conclude.

17 “With GS 7340,” the researchers add, “it should be possible to reduce
18 the total dose of tenofovir, thereby minimizing systemic exposure, while
at the same time increasing antiviral activity.”²³

19 124. Moreover, even though Gilead purportedly abandoned TAF, Gilead filed seven
20 applications for patents on TAF between 2004 and 2005.

21 125. Despite recognizing the safety benefits of TAF, Gilead kept its GS-7340 design on the
22 shelf for years—knowingly exposing patients taking its TDF-containing drug products to greater risks
23 of kidney and bone toxicity.

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²³ Novel tenofovir prodrug preferentially targets lymphatic tissue, Reuters Health Medical News,
June 1, 2005.

1 126. It was not until approximately October 2010—*six years* after Gilead shelved its safer
2 tenofovir prodrug and after Gilead designed combination products Truvada and Atripla to contain TDF
3 rather than safer TAF—that Gilead renewed development of the safer TAF design.

4 127. Once Gilead renewed development of its TAF design, it again touted the benefits of
5 TAF over TDF—as if it had never falsely claimed that TAF could not be “highly differentiated” from
6 TDF.

7 128. Despite having discovered the benefits of TAF before 2001, Gilead repeatedly
8 misrepresented TAF as “new.” The benefits of TAF that Gilead described in 2010 and beyond were
9 known to Gilead years earlier. And the clinical results Gilead achieved with TAF would have been
10 achieved years earlier but for Gilead’s decision to slow-walk and withhold the safer TAF design purely
11 for financial gain.

12 129. In an October 19, 2010 earnings call, Gilead’s Chief Scientific Officer Norbert
13 Bischofberger explained to investors how GS-7340’s safety profile was superior to Viread, particularly
14 with respect to kidney and bone toxicity:

15 7340 is a prodrug that actually delivers more active antivirally active
16 components into the compartment in the body where it’s really needed
17 which means lymphocytes mostly. What that means is you can take a
18 lower dose, and actually our clinical study would indicate 1/6th to 1/10th
19 the Viread dose and you would actually get higher efficacy with less
20 exposure. So we’re looking at this to be used in sub population where
21 people have a concern with Viread, and the one with renal impairment,
22 elderly people that have reduced renal function, and the other population
23 will be adults that have preexisting or suspicion of bone disease,
24 osteoporosis, and that’s where we are initially going to position the
25 compound.²⁴

26 130. Giving a statement at the Capital Markets Healthcare Conference on March 2, 2011,
27 John Milligan, then Gilead’s President and Chief Operating Officer, told investors the real reason
28 Gilead previously refused to design its products to contain safer GS-7340—it did not want to hurt TDF
sales by stepping on its TDF marketing message:

27 ²⁴ Q3 2010 Gilead Sciences Earnings Conference Call – Final, FD (Fair Disclosure) Wire, Oct. 19,
28 2010.

1 One of the reasons why we were concerned about developing 7340 was
2 we were trying to launch Truvada versus Epzicom²⁵ at that time. And to
3 have our own study suggesting that Viread wasn't the safest thing on the
4 market, which it certainly was at the time. ... It didn't seem like the best.
5 It seemed like we would have a mix[ed] message. And in fact that Viread
6 story is split out to be a fairly safe product over the years. There are some
7 concerns still on kidney toxicity and there are some concerns about bone
8 toxicity.²⁶

9 131. Milligan called GS-7340 a "kinder, gentler version of Viread."²⁷

10 132. At the March 14, 2011 Roth Capital Partners Growth Stock Conference, Gilead stated
11 that the ability to dose GS-7340—the "kinder, gentler" version of Viread—lower than Viread was
12 important because GS-7340 is safer, particularly as patients take the medication for the long term.²⁸

13 133. At the NASDAQ OMS 26th Investor Program in June 2011, Gilead described GS-7340
14 as a "very exciting product" which was then in dosing studies to determine just how low GS-7340
15 could be dosed. Gilead explained the benefit of lower dosing to aging patients and those who have
16 been on the medication for a long time:

17 And we had recently this year had presented 14-day monotherapy results
18 from a study we had done at 50 and 100 mg of 7340 versus the 300 mg
19 of Viread today. And what we have shown was viral load reductions
20 were greater in the lower doses of 7340 and the plasma tenofovir levels
21 were actually much reduced from what we see with Viread.

22 We're currently now in a Phase Ib looking at even lower doses. We are
23 studying 8 mg, 25 and 40 mg of GS-7340. This is important because as
24 the age of the AIDS population continues to increase, as the median age
25 is now just about 50 years old, you get issues with aging such as renal
26 function and bone mineral density that can become bigger issues for
27 these patients and we think that it's a currently unmet medical need to
28 address those concerns of the aging population in HIV.²⁹

29 ²⁵ Epzicom is a combination medication, containing abacavir and lamuvidine, indicated to treat
30 HIV sold by Gilead's competitor GlaxoSmithKline, now Viiv Healthcare, Ltd. The FDA approved
31 both Epzicom and Truvada in August 2004.

32 ²⁶ Gilead Sciences at RBC Capital Markets Healthcare Conference – Final, FD (Fair Disclosure)
33 Wire, Mar. 2, 2011.

34 ²⁷ *Id.*

35 ²⁸ Gilead Sciences at Roth Capital Partners OC Growth Stock Conference – Final, FD (Fair
36 Disclosure) Wire, Mar. 14, 2011.

37 ²⁹ Gilead Sciences Inc. at NASDAQ OMS 26th Investor Program – Final, FD (Fair Disclosure)
38 Wire, June 21, 2011.

1 Yet, Gilead knew well before 2010–2011 that people with HIV were living longer lives. Since the
2 introduction of effective combination antiretroviral therapy in late 1995 and early 1996, many people
3 with HIV have lived a normal lifespan.

4 134. On January 24, 2012, Gilead announced that it had begun Phase II clinical trials of GS-
5 7340 and identified a dose that is ten times lower than Viread while providing greater antiviral efficacy.

6 135. On October 31, 2012, Gilead announced that a Phase II clinical trial evaluating TAF
7 met its primary objective. The study compared a once-daily single tablet regimen containing TAF 10
8 mg/elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg with Stribild (TDF 300
9 mg/elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg) among treatment-naïve adults.
10 Compared to Stribild, the TAF-containing regimen demonstrated better markers of bone and kidney
11 effects that were statistically significant. The study showed that TAF is effective at a fraction of the
12 dose of Viread and provides safety advantages.

13 136. In January 2013, Gilead began Phase III clinical development of TAF. Announcing the
14 beginning of Phase III development, then-CEO Martin mischaracterized TAF as “new.”³⁰

15 137. Gilead finally submitted an application to market its first TAF-containing product,
16 Genvoya, to the FDA on November 5, 2014 (though it could have done so years earlier had it not
17 shelved the safer design to make more money).

18 138. When the FDA approved Genvoya on November 5, 2015, John C. Martin, then
19 Chairman and CEO of Gilead, announced that “there is still a need for new treatment options that may
20 help improve the health of people as they grow older with the disease.”³¹ Martin misrepresented that
21 TAF was “new” and concealed that Gilead had known about this safer version of tenofovir for over a
22 decade but purposefully withheld it from the market solely to protect its monopoly profits and extend
23 Gilead’s ability to profit on TAF regimens for the next decade or more.

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25
26 ³⁰ Gilead Sciences at JPMorgan Global Healthcare Conference – Final, FD (Fair Disclosure) Wire,
27 Jan. 7, 2013.

28 ³¹ US FDA approvals Gilead’s Single Table Regiment Genvoya for Treatment of HIV-1 Infection,
Business Wire, Nov. 5, 2015.

1 **F. Gilead withheld its safer TAF design to protect its TDF sales and extend profits on its**
2 **HIV franchise.**

3 139. Gilead first developed and sought FDA approval for its TDF line of products even
4 though it knew TAF was safer.

5 140. Then Gilead shelved its TAF design in 2004 because it did not want to hurt TDF sales
6 by admitting that TDF is unreasonably and unnecessarily unsafe.

7 141. Gilead continued to withhold its TAF design for the next decade. Gilead knew that by
8 withholding the safer TAF design, it could extend the longevity of its HIV drug franchise and make
9 billions two times over: first, with TDF medications until TDF patent expiration, which would begin
10 by no later than 2018, and second, with TAF medications until TAF patent expiration as late as 2032.

11 142. But Gilead also knew that timing was key. While it wanted to delay the TAF-designed
12 products to maximize profits on its TDF Drugs, it also knew that it had to get its TAF-based products
13 on the market sufficiently in advance of TDF patent expiration. Gilead knew that once doctors switched
14 their patients from TDF to TAF, doctors would be highly unlikely to switch their patients back to TDF-
15 based regimens once generic TDF became available. By converting TDF prescriptions to TAF
16 prescriptions (which cannot be automatically substituted at the pharmacy counter with a generic TDF
17 product), Gilead could save a substantial percentage of sales from going generic.

18 143. Only once Gilead had realized billions in sales through most of the TDF patent life—
19 having built Viread sales up to \$1.1 billion and the TDF portfolio up to \$11 billion in sales in 2015—
20 did Gilead create TAF-based versions of its prior TDF Drugs and work to convert its TDF Drug sales
21 to TAF drug sales.

22 144. Once TAF entered the market, Gilead successfully convinced a large percentage of
23 doctors to switch from TDF-based to TAF-based regimens by highlighting TAF's improved safety
24 profile with respect to bone and kidney toxicity—the very benefits that Gilead could have and should
25 have incorporated into its product design from the beginning but withheld from patients with each
26 successive TDF Drug for over a decade.

27 145. In addition, by delaying the filing of an NDA for its first TAF product, for which it
28 received five-year regulatory exclusivity, Gilead knew that it was also delaying the entry of any generic

1 manufacturer who could successfully challenge Gilead’s TAF patents as invalid or not infringed. Due
2 to its regulatory exclusivity, no generic manufacturer can even file an ANDA with a Paragraph IV
3 certification seeking to market a generic version of Genvoya until November 2019 and then, upon
4 Gilead’s suit against the generic, Gilead can automatically delay generic entry by up to an additional
5 30 months.

6 146. Gilead boasted about TAF’s potential to extend its HIV franchise, which has been the
7 core of its business.

8 147. Milligan told investment analysts in 2010 that the safer TAF-designed products could
9 replace the whole TDF franchise which would provide a “great deal of longevity”³² Milligan
10 similarly told investors at a Deutsche Bank Securities Inc. Healthcare Conference in May 2011 that
11 TAF was a “new” drug that “could potentially bring quite a bit of longevity to the Gilead portfolio.”³³

12 148. As Milligan told analysts at a Goldman Sachs Global Healthcare Conference in June
13 2011, Gilead would be “offering a product called 7340, which we believe is a lower dose, better safety
14 profile, more potent, differentiated drug relative to Viread. And so, our ability to develop and get that
15 onto the market prior to [TDF] patent expiration will be key to us, to maintain the longevity.”³⁴

16 149. Gilead withheld its safer TAF design until it suited Gilead’s bottom line at the expense
17 of patients’ health.

18 **G. Gilead knowingly designed its TDF drugs to be unreasonably dangerous and unsafe to**
19 **patients’ kidneys and bones.**

20 150. Despite knowing that TDF causes kidney and bone damage and that TAF is safer for
21 patients’ kidneys and bones, Gilead designed the TDF Drugs to contain TDF rather than safer TAF as
22 the orally available version of tenofovir.

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25 ³² Gilead Sciences at 22nd Annual Piper Jaffray Healthcare Conference – Final, FD (Fair
Disclosure) Wire, Nov. 30, 2010.

26 ³³ Gilead Sciences Inc. at Deutsche Bank Securities Inc. Health Care Conference – Final, FD (Fair
Disclosure) Wire, May 3, 2011.

27 ³⁴ Gilead Sciences Inc. at Goldman Sachs Global Healthcare Conference – Final, FD (Fair
28 Disclosure) Wire, June 7, 2011.

1 151. In addition to withholding the safer TAF design of Stribild, Gilead made Stribild even
2 more dangerous to patients when it formulated the drug to include 300 mg TDF with cobicistat.

3 152. Stribild is a fixed dose combination containing 300 mg TDF, emtricitabine, elvitegravir,
4 and cobicistat. Elvitegravir is an integrase strand transfer inhibitor (INSTI). Cobicistat has no
5 antiretroviral effect; it is a pharmacoenhancer that increases the plasma concentrations of elvitegravir.
6 Regimens that include a pharmacoenhancer like cobicistat are called “boosted” regimens.

7 153. Gilead’s early development of elvitegravir used ritonavir as the boosting agent. Gilead
8 knew before Viread entered the market in 2001 that coadministration of TDF with ritonavir-boosted
9 lopinavir significantly increased tenofovir concentrations. By 2004, the Viread label warned doctors
10 to carefully monitor patients taking both TDF and ritonavir/lopinavir. And scientific literature
11 published years before Gilead developed Stribild indicated that renal toxicity associated with TDF was
12 more frequent in patients receiving TDF in combination with boosted protease inhibitors.

13 154. Although Gilead ultimately replaced ritonavir with cobicistat as the boosting agent in
14 Stribild, the two boosters are structurally similar. Gilead learned during development of Stribild that
15 tenofovir levels in patients receiving Stribild (TDF with cobicistat) were similar to the tenofovir levels
16 experienced in patients who took TDF in combination with a ritonavir-boosted protease inhibitor.
17 Gilead knew that tenofovir levels are 25–35% higher when combining TDF in a boosted regimen.

18 155. Despite knowing that combining TDF with cobicistat would significantly increase
19 tenofovir levels in patients’ blood, Gilead did not reduce the dose of TDF when it formulated Stribild.
20 Gilead’s Stribild clinical trials showed an increased rate of serious renal adverse events that led to
21 treatment discontinuation. Stribild is even more toxic to patients’ kidneys and bones than unboosted
22 TDF.

23 156. When Gilead formulated its first TAF-based drug, Genvoya—which was Stribild with
24 TAF in place of TDF—Gilead reduced the dose of TAF to account for the fact that cobicistat increases
25 tenofovir concentrations. A Phase I TAF dosing trial showed that TAF 25 mg was the optimal dose to
26 achieve activity similar to a 300 mg dose of TDF. When formulating Genvoya, however, Gilead further
27 reduced the TAF dose to 10 mg because, when given with cobicistat, TAF 10 mg achieves exposure
28 similar to TAF 25 mg when given without cobicistat.

1 157. Gilead knew to reduce the dose of TAF to 10 mg when given with cobicistat before
2 Gilead sought FDA approval for Stribild. Pursuant to Gilead’s Phase I study GS-US-311-0101,
3 conducted between June 6, 2011 and August 31, 2011, Gilead determined that co-administration of
4 TAF with cobicistat significantly increased the body’s exposure to TAF and active tenofovir. It found
5 that the body’s drug exposure across time (known as the “area under the curve” in pharmacokinetic
6 parlance) increased 2.7-fold with respect to TAF and 3.3-fold with respect to tenofovir when given
7 with cobicistat. Gilead addressed this drug interaction by reducing the dose of TAF from 25 mg to 10
8 mg in the Genvoya tablet. When Gilead began its study GS-US-292-0103 on October 5, 2011, it used
9 a TAF dose of 10 mg in the Genvoya combination because “the TAF dose is 10 mg when combined
10 with COBI in the [fixed dose combination] versus 25 mg when not combined with COBI.”³⁵

11 158. Critically, Gilead reduced the TAF dose when formulating Genvoya even though
12 patients’ plasma exposure to tenofovir when taking TAF is already significantly less than their
13 tenofovir exposure when taking TDF due to TAF’s enhanced entry and absorption into target cells.

14 159. Moreover, in July 2011, months before Gilead submitted its Stribild NDA to the FDA,
15 Gilead sought FDA approval of reduced doses of TDF (Viread) in 150 mg, 200 mg, and 250 mg
16 strengths for the treatment of HIV-1 infection in pediatric patients ages 2-12. That same month, Gilead
17 also sought approval of Viread 40 mg oral powder for the treatment of HIV-1 infection in pediatric
18 patients 2 years and older.³⁶ The FDA approved the lower dosage strength TDF tablets and oral powder
19 in early January 2012—over six months before the FDA approved the Stribild NDA. There was no
20 reason Gilead could not have similarly reduced the dose of TDF in Stribild—when it knew that failing
21 to reduce the dose would increase the drug’s toxicity.

22 160. As a direct result of Gilead’s decision not to use a safer design, Stribild proved to be
23 toxic to patients’ kidneys and bones.

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26 ³⁵ FDA Center for Drug Evaluation and Research, Genvoya NDA 207561 Clinical Pharmacology
27 and Biopharmaceutics Review(s) at 32, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207561Orig1s000ClinPharmR.pdf.

28 ³⁶ In the EU, Gilead recommends that adults with creatinine clearance below 50 mL/min take Viread oral powder to reduce their doses of TDF.

1 161. In the clinical trials of Stribild over 48 weeks, eight patients in the Stribild group
2 compared to one in the comparator groups discontinued the drug study due to renal adverse events,
3 including kidney failure and Fanconi Syndrome. Four of these patients developed laboratory findings
4 consistent with proximal renal tubular dysfunction. The laboratory findings in these four subjects
5 improved but did not completely resolve upon discontinuation of Stribild. The signature toxicity of the
6 Stribild group was proximal renal tubular dysfunction.

7 162. The FDA’s Medical Review described the notable adverse events that led to study
8 discontinuation more frequently in the Stribild group as a “constellation of renal [Adverse Events] (e.g.
9 renal failure, Fanconi syndrome, and increased blood creatinine).”³⁷

10 163. According to the FDA, the “most important safety risks of Stribild use are associated
11 with two key toxicities: renal adverse events (particularly proximal renal tubular dysfunction) and bone
12 toxicity. Both of these events have previously been associated with use of TDF”³⁸

13 164. The FDA noted that “published literature suggests that the renal toxicity associated with
14 TDF may be more frequent in patients receiving TDF in combination with PIs, including ritonavir,”³⁹
15 and the “review team remains concerned that COBI may exacerbate the known renal toxicity
16 associated with TDF.”⁴⁰ In its Summary Review of the Stribild NDA, the FDA concluded: “it appears
17 that the combination of COBI with TDF may have more renal toxicity than TDF alone as highlighted
18 in the clinical reviews and the renal consult.”⁴¹ The FDA expressed concern that the data reviewed for
19 the Stribild NDA represented an increased hazard signal even compared to regimens containing TDF
20 combined with another boosting agent.

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23 ³⁷ FDA Center for Drug Evaluation and Research Stribild NDA 203100 Medical Review at 9,
available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203100Orig1s000MedR.pdf.

24 ³⁸ FDA Center for Drug Evaluation and Research Stribild NDA 203100 Cross Discipline Team
25 Member Review at 17, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203100Orig1s000CrossR.pdf.

26 ³⁹ *Id.* at 18.

27 ⁴⁰ *Id.*

28 ⁴¹ FDA Center for Drug Evaluation and Research Stribild NDA 203100 Summary Review at 16,
available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203100Orig1s000SumR.pdf.

1 165. Due to Stribild’s renal toxicity, Stribild use is restricted in patients with impaired renal
2 function. Stribild’s label states that doctors should not initiate Stribild in patients with estimated
3 creatinine clearance below 70 mL per minute, and Stribild should be discontinued if estimated
4 creatinine clearance declines below 50 mL per minute as dose interval adjustment cannot be achieved.
5 Moreover, in the EU—though not in the U.S.—Gilead warns doctors that Stribild should not be
6 initiated in patients with creatinine clearance below 90 mL per minute unless, after review of all
7 available treatment options, it is considered that Stribild is the preferred treatment for the individual
8 patient.

9 166. Gilead’s post-approval Stribild data continued to show renal adverse effects. In the
10 clinical trials of Stribild over 96 weeks, two additional Stribild patients discontinued the study due to
11 a renal adverse reaction. In the clinical trials of Stribild over 144 weeks, three additional Stribild
12 patients discontinued the study due to a renal adverse reaction. In addition, one patient who received
13 ritonavir-boosted atazanavir plus Truvada (i.e., a boosted TDF regimen) in the comparator group
14 developed laboratory findings consistent with proximal renal tubular dysfunction leading to drug
15 discontinuation after week 96.

16 **H. Gilead obtained FDA approval for its TAF-based products by relying on studies**
17 **demonstrating TAF’s superiority over TDF.**

18 167. In seeking FDA approval of its first TAF-based antiviral drug product, Genvoya, Gilead
19 told the FDA that TAF has better entry and concentration in HIV-target cells than TDF, thereby
20 allowing the administration of smaller doses and reducing systemic tenofovir exposure, renal toxicity
21 and bone effects, without sacrificing efficacy.

22 168. Gilead established during Phase I clinical development of TAF that doses as low as 8
23 to 25 mg of TAF had antiviral activity comparable to the approved dose of TDF 300 mg. Gilead
24 selected the 25 mg TAF dose as the optimal dose for Phase 2 and 3 studies based on its antiviral
25 activity. Gilead included TAF 10 mg in Genvoya because it provides similar exposures to TAF 25 mg
26 when coadministered with cobicistat.

27 169. Gilead supported the safety and efficacy of Genvoya with two clinical trials that
28 compared Genvoya to its TDF-containing counterpart, Stribild. In those studies, a 10 mg oral dose of

1 TAF in Genvoya resulted in greater than 90% lower concentrations of active tenofovir in plasma as
2 compared to a 300 mg oral dose of TDF in Stribild. Due to these lower plasma concentrations, Gilead
3 expected that the kidney and bone toxicities associated with TDF would occur at a lower rate with
4 TAF. And, as expected, the trials showed that rates of biomarkers for tenofovir-induced renal and bone
5 toxicities were less with Genvoya than Stribild.

6 170. In seeking FDA approval of Genvoya in 2014, Gilead relied on TAF data obtained by
7 Gilead more than a decade earlier—before the company abruptly shelved its TAF design in pursuit of
8 more money. Gilead submitted in its Genvoya NDA data from: (a) early clinical development showing
9 that TAF provided greater intracellular distribution of tenofovir yielding lower plasma tenofovir levels
10 than TDF; (b) preclinical studies that indicated TAF is less likely to accumulate in renal proximal
11 tubules, supporting the potential for an improved renal safety profile; and (c) Phase I dosing studies
12 supporting doses of TAF far lower than the standard 300 mg dose of TDF.

13 171. Reviewing these studies, the FDA stated that: “Based on the design of the pivotal
14 clinical trials, safety can be directly compared between TAF (Genvoya) and TDF (as Stribild) in
15 subjects initiating treatment.”⁴² According to the FDA, the studies showed that “the rates of signature
16 TFV [tenofovir] toxicities related to bone mineral density and renal laboratory parameters were lower
17 [than TDF], likely due to the fact that the TAF prodrug yields lower plasma concentrations of TFV.”⁴³

18 172. As a result of its improved renal safety profile over TDF, Gilead’s TAF-containing
19 products are better tolerated by patients with renal impairment.

20 173. For example, Genvoya requires no dosage adjustment for patients with creatinine
21 clearance greater than or equal to 30 mL per minute, whereas its TDF-containing counterpart Stribild
22 is not recommended for patients with creatinine clearance below 70 mL per minute and Stribild should
23 be discontinued if creatinine clearance falls below 50 mL per minute as dose interval adjustment cannot
24 be achieved. Due to its superior safety profile, Genvoya has an expanded indication for renally
25 impaired individuals with creatinine clearance greater than or equal to 30 mL per minute.

26 _____
27 ⁴² FDA Center for Drug Evaluation and Research Genvoya NDA 207561 Summary Review at 10,
28 available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207561Orig1s000SumR.pdf.

⁴³ *Id.* at 15.

1 174. As a result of its improved bone toxicity safety profile over TDF, the labels for Gilead’s
2 TAF-containing products no longer include bone effects in the Warnings and Precautions sections of
3 those labels.

4 175. The FDA agreed that bone effects need only be displayed in the Adverse Events section
5 of TAF drug labeling because “[w]ith respect to bone toxicity, TAF appears to have substantially less
6 of an adverse effect on bone mineral density (BMD) than TDF.”⁴⁴

7 176. Gilead removed bone toxicity from the Warnings and Precautions sections of the
8 Genvoya label in December 2016 and from the Odefsey and Descovy labels in 2017. Bone toxicity
9 remains in the Warnings and Precautions sections of the labels of Gilead’s TDF Drugs to this day.

10 **I. Gilead markets TAF as superior to TDF.**

11 177. Gilead’s TAF-based product websites, including the Genvoya site, market the TAF-
12 based drugs as superior to Gilead’s TDF-containing products with respect to kidney health. Gilead
13 recognizes that: “Kidneys play a key role in keeping you healthy, working around the clock to remove
14 waste from your blood. That’s why it’s so important to take care of them, especially if you have HIV-
15 1.”⁴⁵ Gilead states that the TAF-based products have “less impact on kidney lab tests” than other
16 approved HIV-1 treatments, including Stribild, Atripla, and Truvada. The website also highlights that
17 unlike its TDF products, the TAF-based products are “FDA-approved for people with mild-to-
18 moderate kidney problems and can be used in some people with lowered kidney function without
19 changing the dose.”⁴⁶

20 178. Gilead’s TAF-based product websites, including the Genvoya site, market the TAF-
21 based drugs as superior to Gilead’s TDF-containing products with respect to bone health. Gilead
22 recognizes that: “Because HIV-1 medicines may impact your bones, it’s important to protect your bone
23 health. If you’re under 30 years of age, you’re still developing bone mass. If you’re over 30, your
24

25 ⁴⁴ FDA Center for Drug Evaluation and Research Vemlidy NDA 208464 Summary Review at 5,
26 available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208464Orig1s000SumR.pdf.

27 ⁴⁵ See <https://www.genvoya.com/hiv-kidney-bone-health>.

28 ⁴⁶ *Id.*

1 bones have fully developed and it's important to try to maintain them.”⁴⁷ The site touts clinical studies
2 which demonstrate that the TAF-containing products “had less impact on hip and lower spine bone
3 mineral density than the other approved HIV-1 treatments,” including Stribild, Atripla, and Truvada.⁴⁸

4 179. Gilead also touts TAF as safer than TDF to scientists, clinical investigators, and doctors
5 attending the annual Conference on Retroviruses and Opportunistic Infections (“CROI”).

6 180. In 2015, Gilead scientists presented to CROI attendees data evaluating the safety and
7 efficacy of Genvoya in patients with mild to moderate renal impairment. Gilead stated that “TDF has
8 been associated with clinically significant renal and bone toxicity,” and “[r]elative to TDF 300 mg,
9 TAF at an equivalent dose of 25 mg has 90% lower circulating plasma TFV, while maintaining high
10 antiviral activity.”⁴⁹ This first study of a single-tablet antiviral regimen without dose adjustment in
11 patients with mild to moderate renal impairment demonstrated the efficacy and renal and bone safety
12 of Genvoya in this patient population.

13 181. In 2016, Gilead scientists presented to CROI attendees data evaluating the renal safety
14 of TAF in patients with a high risk of kidney disease. Gilead stated that TDF “has been associated with
15 an increased risk of [chronic kidney disease]” and “[d]ue to a 91% lower plasma tenofovir level,
16 tenofovir alafenamide (TAF) relative to TDF has demonstrated a significantly better renal safety
17 profile and no discontinuations due to renal adverse events through 2 years in 2 randomized, double-
18 blind studies ... comparing TAF to TDF”⁵⁰ With respect to high risk renal patients, Gilead
19 concluded that “[a]ntiretroviral-naïve adults with both high and low risk for [chronic kidney disease]
20 treated with TAF had more favorable renal outcomes compared to those treated with TDF.”⁵¹

21 182. Gilead also presented at the 2016 CROI data demonstrating that TAF is safer to kidneys
22 than TDF in the longer-term. Showing data through 96 weeks, Gilead concluded that “[c]linically
23

24 ⁴⁷ *Id.*

25 ⁴⁸ *Id.*

26 ⁴⁹ <http://www.croiconference.org/sites/default/files/posters-2015/795.pdf>.

27 ⁵⁰ <http://www.croiconference.org/sites/default/files/posters-2016/681.pdf>.

28 ⁵¹ *Id.*

1 significant renal events were less frequent in patients receiving” TAF vs. TDF and these “data provide
2 further support for the improved renal safety profile of TAF compared with TDF.”⁵²

3 183. In 2017, Gilead scientists presented to CROI attendees data showing that switching
4 patients with low bone mineral density from a TDF-based to a TAF-based regimen results in increased
5 BMD and a reversion from osteoporosis, leading Gilead to conclude that “[s]witching from TDF to
6 TAF may be an important treatment strategy to increase bone mineral density in those at the highest
7 fracture risk.”⁵³

8 184. Also in 2017, Gilead scientists presented to CROI attendees 144-week data establishing
9 the superiority of TAF over TDF with respect to efficacy as well as kidney and bone safety. At week
10 144, TAF: was “superior to [TDF] on virologic efficacy,” had “significantly less impact than [TDF]
11 on renal biomarkers,” and had “significantly less impact than [TDF] on BMD.”⁵⁴

12 185. In 2018, Gilead scientists presented to CROI attendees 96-week data that showed that
13 switching to a TAF-based regimen resulted in “significant increases in bone mineral density at hip and
14 spine” and “improved biomarkers of renal tubular function.”⁵⁵

15 186. Gilead’s sales force has used data showing the superior safety profile of TAF over TDF
16 to convince doctors to switch patients from TDF-based to TAF-based products.

17 187. Gilead President and COO Milligan told analysts during a November 10, 2015 Credit
18 Suisse Healthcare Conference that he expected Gilead’s sales representatives to be successful in
19 switching the market from TDF to Genvoya based on favorable data showing the benefits of TAF over
20 TDF. Milligan viewed switching patients from Stribild to Genvoya as “the most likely thing to happen
21 very commonly, because it’s very seamless for the patient. You’re not really changing much; you’re
22 just getting a better version of Stribild.”⁵⁶ Milligan also touted the benefit of switching Atripla patients,
23

24 _____
25 ⁵² <http://www.croiconference.org/sites/default/files/posters-2016/682.pdf>.

26 ⁵³ http://www.croiconference.org/sites/default/files/posters-2017/683_Brown.pdf.

27 ⁵⁴ http://www.croiconference.org/sites/default/files/posters-2017/453_Arribas.pdf.

28 ⁵⁵ http://www.croiconference.org/sites/default/files/posters-2018/1430_Mills_504.pdf.

⁵⁶ Gilead Sciences Inc. at Credit Suisse Healthcare Conference – Final, FD (Fair Disclosure) Wire,
Nov. 10, 2015.

1 who, at that point, had a decade of TDF toxicity buildup, to Genvoya, which, he said, gives patients
2 the benefits of TDF with a better safety profile.

3 188. In order to prevent or combat the cumulative buildup of kidney and bone toxicity
4 associated with TDF (which Gilead itself caused by withholding the safer TAF design), Gilead’s
5 message was: “if you’re a new patient, start with a TAF-based single-tablet regimen, because that’s
6 going to be highly efficacious and very safe and very tolerable for long-term usage. And if you’re on
7 a Viread-based regimen, it’s a great idea to convert, switch, upgrade to a TAF-based regimen as soon
8 as possible.”⁵⁷

9 189. According to Milligan, Genvoya was the most successful launch ever for an HIV
10 therapy. After six months on the market, Genvoya was the most prescribed regimen for treatment-
11 naïve and switch patients.

12 190. Gilead’s conversion strategy continued with FDA approval of Gilead’s subsequent
13 TAF-based products. As Milligan stated in March 2016, the marketplace was moving to TAF because
14 patients need the safest possible medication:

15 [A]s I look at TAF right now there’s a very strong medical rationale for
16 TAF versus Viread. And so what we’re seeing in the marketplace with
17 the launch of Genvoya and then with the recent approval of Odefsey is
18 the desire to move patients from a TDF containing regimen to a TAF
19 containing regimen . . . it’s very interesting that the field wants to move
20 to the safest medication, I think should move to the safest medication
21 because it’s a great opportunity for patients to stay on care for another
22 10 to 20 years which is really where we’re at with most of these patients.
23 They’re going to need decades more care and so you need the gentlest,
24 safest option for patients⁵⁸

25 191. Gilead’s 2017 Annual Report attributes strong growth in its HIV business to
26 “widespread physician acceptance and uptake” of the TAF-based regimens.⁵⁹

27 ⁵⁷ Gilead Sciences Inc. at Piper Jaffray Healthcare Conference – Final, FD (Fair Disclosure) Wire,
28 Dec. 1, 2015.

⁵⁸ Gilead Sciences Inc. at Barclays Global Healthcare Conference – Final, FD (Fair Disclosure)_
Wire, Mar. 15, 2016.

⁵⁹ Gilead Sciences 2017 Year in Review at 7, available at <https://www.gilead.com/-/media/files/pdfs/yir-2017-pdfs/final-year-in-review-426.pdf?la=en&hash=E86C6471302682C56A548CC42342AFC4>.

1 192. In January 2018, Milligan stated that “physicians and patients prefer TAF dramatically
2 over our TDF-containing backbones,” noting that its TAF-based products had achieved more than 56%
3 of the market share of its TDF-containing regimen.⁶⁰ TAF-based products now make up at least 74%
4 of Gilead’s TDF- and TAF-based drug products for HIV treatment.

5 193. Gilead could have and should have incorporated the benefits of TAF, which doctors
6 and patients “prefer dramatically” over TDF, into its products years earlier.

7 194. Gilead funded a 2018 study, Baumgardner, J., *et al.*, “Modeling the impacts of
8 restrictive formularies on patients with HIV,” that highlights the damage Gilead did by withholding
9 TAF products from the market. The authors found that a restrictive drug formulary design,⁶¹ which
10 restricts access to TAF or TDF-sparing regimens (other antiviral drugs, abacavir, lamuvidine, and
11 douletegravir), forcing more people to use TDF-containing regimens, would cause 171,500 more
12 cumulative bone and renal events and 16,500 more deaths by 2025 compared to an open formulary
13 design which permitted patients to start on TAF. Gilead itself prevented patients from taking TAF for
14 more than a decade—longer than the period covered by the 2018 study. Gilead likely caused even
15 more deaths and injuries as a result of its callous decision to withhold the safer TAF drugs.

16 **J. Gilead failed to adequately warn about the risks of TDF.**

17 195. In addition to withholding a safer TAF-based design despite knowing the risk its TDF
18 Drugs posed to patients’ kidneys and bones, Gilead failed to adequately warn physicians and patients
19 about the risks and safe use of TDF.

20 **1. Gilead failed to adequately warn doctors about the risks of TDF.**

21 196. Because tenofovir is primarily cleared out of the body by the kidneys, a patient
22 experiences even greater exposure to tenofovir as the kidneys become impaired—causing even greater
23 harm. As a result, early detection is key to preventing serious, potentially irreversible renal injury.
24 Frequent monitoring for TDF-induced toxicity is also critical because patients are typically
25

26
27 ⁶⁰ Gilead Sciences Inc. at JPMorgan Healthcare Conference – Final, FD (Fair Disclosure) Wire,
Jan. 8, 2018.

28 ⁶¹ A drug formulary is a list of an insurer’s covered drugs and is designed to save money.

1 asymptomatic in the early stages. Gilead, however, downplayed the risks of TDF and the need to
2 carefully monitor all patients in order to inflate sales.

3 197. During the first years Viread was on the market, Gilead relied on Viread sales for a
4 significant portion of its operating income. For 2002, Viread's first full year on the market, Viread
5 sales comprised 53% of Gilead's total product sales. In 2003, Viread accounted for 68% of Gilead's
6 total product sales.

7 198. Gilead stated in its 2002 10-K that its operations would suffer if Viread did not maintain
8 or increase its market acceptance. Gilead also stated that if additional safety issues were reported for
9 Viread, this could "significantly reduce or limit our sales and adversely affect our results of
10 operations."⁶² Gilead made similar statements in its 2003 and 2004 10-K filings.

11 199. To make sure that safety issues did not depress or slow the growth of Viread sales,
12 which were crucial to Gilead's operations, Gilead dramatically increased its sales force and marketing
13 budget, and trained its sales representatives to deceptively represent Viread's safety profile. At the
14 direction of Gilead's senior management, Gilead representatives told doctors that Viread was a
15 "miracle drug," "extremely safe," and "extremely well-tolerated" with "no toxicities." Gilead's sales
16 representatives did not tell doctors the facts: that Viread posed significant risks to patients' kidneys
17 and bones.

18 200. According to a 2009 shareholder lawsuit filed against Viread, Viread's then-Chief
19 Executive Officer John C. Martin frequently referred to Viread as a "miracle drug" at sales force
20 meetings. According to a former employee, Gilead was trying to overcome the perception in the
21 medical community that Viread was like Gilead's previous HIV drugs and would likely cause kidney
22 damage.

23 201. On March 14, 2002, FDA sent Gilead a Warning Letter admonishing Gilead for
24 engaging in promotional activities that contained false and misleading statements in violation of the
25
26

27 _____
28 ⁶² Gilead Sciences, Inc. Form 10-K for the fiscal year ended Dec. 31, 2002 at 24 available at
<https://www.sec.gov/Archives/edgar/data/882095/000104746903008695/a2105292z10-k.htm>.

1 Federal Food, Drug and Cosmetic Act. The FDA stated that Gilead unlawfully minimized Viread's
2 risks, including with respect to kidney toxicity, and overstated its efficacy.

3 202. Despite this warning, Gilead continued to unlawfully promote Viread by minimizing
4 its safety risks. During a June 2003 sales force training, Gilead instructed sales representatives to
5 respond to anticipated physician concerns about Viread's nephrotoxicity by downplaying that many
6 patients taking Viread had experienced the adverse effects of kidney toxicity—some of them severe
7 —including but not limited to renal failure, acute renal failure, Fanconi syndrome, proximal
8 tubulopathy, increased creatinine, and acute tubular necrosis. Gilead's sales representatives omitted
9 this material information from their sales presentations in order to drive sales.

10 203. The FDA issued another Warning Letter to Viread on July 29, 2003, stating that
11 Gilead's sales representatives had repeatedly omitted or minimized material facts regarding the safety
12 profile of Viread. Among other things, the FDA required Gilead to retrain its sales force to ensure that
13 Gilead's promotional activities complied with the Federal Food, Drug and Cosmetic Act and
14 accompanying regulations. But Gilead had achieved its goal: rapidly increased Viread sales.

15 204. In subsequent years, Gilead continued to downplay the risks of TDF-induced toxicity
16 when promoting its TDF Drugs to doctors by withholding information about the frequency and severity
17 of adverse kidney and bone events; dismissing case reports of acute renal failure and other TDF-
18 associated adverse events as purportedly unavoidable side effects of tenofovir in an otherwise "safe"
19 drug; and failing to tell doctors to monitor patients for drug-induced toxicity using more sensitive
20 markers of kidney function.

21 205. In addition to omitting crucial facts about the safety profile of TDF when promoting
22 TDF to doctors, Gilead also downplayed the importance of patient monitoring in its TDF Drug labeling
23 despite the importance of early detection of TDF-induced toxicity. The dangerous inadequacies in
24 Gilead's drug labeling were compounded by the misleading marketing messages it gave to doctors.

25 206. From Viread's product approval on October 26, 2001, through May 20, 2007, Gilead's
26 TDF labeling failed to warn doctors that all patients needed to be monitored for adverse kidney effects.
27 During this time, Gilead only recommended monitoring patients taking TDF Drugs for renal adverse
28 effects if patients were at risk for, or had a history of, renal impairment or if they were taking another

1 nephrotoxic drug. This monitoring recommendation was woefully inadequate because, as Gilead was
2 well aware, TDF-associated renal toxicity had harmed patients who were not at risk for, or did not
3 have a history of, renal impairment.

4 207. Gilead failed to include any warning about the need to monitor bone effects until
5 October 14, 2003, and that warning was limited to patients with certain risk factors. Since then, Gilead
6 has only suggested that doctors monitor, and only informs patients that monitoring may be necessary,
7 for patients with certain risk factors for bone adverse effects. Gilead's inadequate kidney monitoring
8 warnings also prevented doctors from detecting early signs of kidney damage that can lead to bone
9 density loss.

10 208. Gilead failed to warn about the need for universal monitoring even though it knew that
11 all patients taking TDF are at risk for renal and bone adverse effects.

12 209. Gilead failed to warn about the need for universal monitoring even after patients
13 without preexisting risk factors experienced kidney and bone effects.

14 210. Gilead failed to warn about the need for universal renal monitoring even though patients
15 with a certain level of renal impairment should not take its TDF products or, if TDF products are to be
16 administered to certain renally impaired patients, the dosing interval must be adjusted. The Viread and
17 Truvada labels require a dosing interval adjustment for patients with creatinine clearance of 30–49 mL
18 per minute, and Atripla and Complera cannot be taken by patients with a creatinine clearance of less
19 than 50 mL per minute. Frequent monitoring of all patients' kidney function is necessary to ensure that
20 patients' kidneys are healthy enough to continue treatment or patients receive a needed dose interval
21 adjustment.

22 211. Presented with signs of nephrotoxicity, physicians could have weighed further
23 treatment options, such as increased monitoring, less frequent dosing, or drug discontinuation, before
24 the damage manifested, worsened, or became irreversible. By failing to warn doctors to monitor all
25 patients for TDF-associated toxicity, Gilead delayed the diagnosis of TDF-associated harm, causing
26 or enhancing injuries that would have been prevented or lessened through early detection.

27 212. On May 21, 2007, Gilead added to the Viread label a recommendation that doctors
28 calculate creatinine clearance (one measure of kidney function) in all patients before initiating

1 treatment with a TDF-based product and as clinically appropriate during therapy. Gilead recommended
2 monitoring of creatinine clearance and serum phosphorus only for patients at risk for renal
3 impairment.⁶³

4 213. The “all patients” monitoring recommendation for Viread, Truvada, Atripla, and
5 Complera remained inadequate because it instructed doctors to assess just one, insufficiently sensitive
6 marker of kidney function.⁶⁴ Without using sufficiently sensitive markers of kidney function,
7 substantial kidney injury can occur before it is measurable. As a result, the detection of TDF-induced
8 nephrotoxicity often comes too late, resulting in kidney injury that may be irreversible. Gilead should
9 have warned doctors to test all patients for additional markers of kidney function, such as serum
10 phosphorus and/or urine glucose, which are more sensitive to changes in the nephron tubule, the main
11 site of TDF damage.⁶⁵

12 214. Phosphorus is a mineral that plays an important role in many physiologic systems,
13 including keeping bones healthy and strong. Normal working kidneys maintain balanced levels of
14 phosphorus in the blood. Low levels of phosphorus in the blood may be indicative of impaired kidney
15 function. Moreover, low serum phosphate is itself dangerous; low levels of phosphorus in the blood
16 can cause a range of health problems, including serious bone and heart damage.

17 215. Serum phosphorus is a more sensitive marker of nephron tubule function than creatinine
18 clearance. The nephron tubule is responsible for reabsorbing phosphorus from the glomerular filtrate.

19
20 ⁶³ Gilead did not add similar warnings to the Truvada and Atripla labels until 2008. Complera’s
21 label included such a warning at the time of FDA approval in 2011. And when Gilead began marketing
22 Stribild in 2012, it warned doctors to assess some measures of kidney function in all patients but failed
to warn doctors to monitor all patients for serum phosphorus. These warnings remained inadequate.

23 ⁶⁴ It was not until 2018 that Gilead strengthened the Truvada, Atripla, and Complera labels to
24 recommend that all patients receive monitoring for serum creatinine, estimated creatinine clearance,
urine glucose, and urine protein. Gilead did not make this change to the Viread label until December
2018, after Plaintiffs filed suit.

25 ⁶⁵ The “all patients” monitoring recommendation for Stribild upon approval was inadequate
26 because it failed to warn doctors to measure serum phosphorus. On August 30, 2017, Gilead
27 strengthened the Stribild label to recommend that all patients be monitored for serum creatinine, serum
28 phosphorus, estimated creatinine clearance, urine glucose, and urine protein. But, on August 8, 2018,
Gilead again weakened the Stribild label to warn doctors to monitor serum phosphorus only in patients
with chronic kidney disease.

1 When the nephron tubule is damaged, it cannot reabsorb enough phosphorus, allowing the phosphorus
2 to be excreted via urine. TDF nephrotoxicity is generally characterized by tubular dysfunction that
3 precedes a decline in glomerular filtration. Thus, by monitoring patients' serum phosphorus, doctors
4 are able to pick up more subtle changes in kidney function that would otherwise go undetected.
5 Moreover, TDF-induced bone injuries are related to the wasting of minerals through the urine. This is
6 due to dysfunction in the nephron tubule, which prevents reabsorption of minerals from the glomerular
7 filtrate. If physicians knew earlier that their patients' kidneys were dysfunctional, subsequent bone
8 injuries could be avoided.

9 216. Presented with early signs of nephrotoxicity, physicians could have weighed further
10 treatment options, such as increased monitoring or drug discontinuation, before the damage
11 manifested, worsened, or became irreversible. By failing to warn doctors to monitor additional, more
12 sensitive markers of all patients' kidney function, Gilead delayed the diagnosis of TDF-associated
13 harm, causing or enhancing patients' injuries that would have been prevented or lessened through early
14 detection.

15 217. Gilead's "all patients" monitoring recommendation for its TDF Drugs also remains
16 inadequate because it fails to instruct doctors how frequently doctors should assess patients' kidney
17 function. By the time a doctor assesses a patient's kidney function when "clinically appropriate," the
18 patient is likely to have already experienced adverse toxic effects, some of which might be irreversible.
19 Regularly scheduled, frequent monitoring of kidney function is necessary to catch early signs of TDF-
20 induced toxicity and prevent injury because patients are generally asymptomatic during the early
21 stages.

22 218. Moreover, after May 21, 2007, the TDF labels do not disclose that adverse kidney and
23 bone events occurred in patients without preexisting risk factors—which, combined with the warning
24 to only routinely monitor patients at risk—gives the false impression that TDF is only harmful to
25 people otherwise at risk for kidney and bone injuries. By failing to warn doctors as to the frequency of
26 monitoring, Gilead delayed the diagnosis of TDF-associated harm, causing or enhancing injuries that
27 could have been prevented or lessened through early detection.

1 219. Gilead’s monitoring instructions for at risk patients taking Viread, Truvada, Atripla,
2 and Complera, and patients taking Stribild are also inadequate because they fail to recommend a
3 specific, frequent monitoring schedule for doctors to assess patients’ kidney function.

4 220. Gilead’s warnings about the need to monitor patients for the renal effects of TDF in the
5 U.S. are far weaker than those given by Gilead to physicians and patients in the European Union. From
6 the approval of the first TDF product in the EU, Gilead’s European labeling (known there as the
7 Summary of Product Characteristics or “SmPC”) has recommended that doctors in the EU routinely
8 monitor, on a specific schedule, all patients taking TDF Drugs for adverse renal effects. In addition,
9 Gilead’s “all patient” monitoring instruction in the EU is not limited to testing only for creatinine
10 clearance. In its EU labeling, Gilead recommends that doctors also monitor all TDF Drug patients’
11 serum phosphorus levels on the specified, frequent schedule.

12 221. Gilead’s renal monitoring instructions for Viread upon approval in the U.S. and the EU
13 looked like this—with Gilead warning EU physicians to monitor all patients’ serum creatinine and
14 serum phosphate at baseline and every four weeks, while it told U.S. doctors to consider monitoring
15 only patients at risk, with no recommended frequency:

Viread U.S. Label 10/26/01	Viread EU Label 02/07/2002
<p>16 Although tenofovir-associated renal toxicity has 17 not be observed in pooled clinical studies for up 18 to one year, long term renal effects are unknown. 19 <u>Consideration should be given to monitoring</u> 20 <u>for changes in serum creatinine and serum</u> 21 <u>phosphorus in patients at risk or with a</u> <u>history of renal dysfunction.</u></p>	<p>22 Although no significant nephrotoxicity has been 23 observed in clinical trials ... the monitoring of 24 renal function is recommended since 25 nephrotoxicity of tenofovir cannot be strictly 26 excluded. <u>The monitoring of renal function</u> <u>(serum creatinine and serum phosphate) is</u> <u>recommended at baseline before taking</u> <u>tenofovir disoproxil fumarate and at routine</u> <u>intervals during therapy every four weeks.</u></p>

22 222. Gilead’s EU label also instructed physicians when to increase monitoring and consider
23 treatment interruption in light of the results of frequent monitoring. Gilead’s U.S. label contained no
24 such warning:

Viread U.S. Label 10/26/01	Viread EU Label 02/07/2002
	<p>26 If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) 27 or serum creatinine is > 1.7 mg/dl (150 μmol/l), 28 renal function should be re-evaluated within one week. Consideration should be given to</p>

Viread U.S. Label 10/26/01	Viread EU Label 02/07/2002
	interrupting treatment with tenofovir disoproxil fumarate in patients with increases in serum creatinine to > 2.0 mg/dl (177 μ mol/l) or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).

223. On December 8, 2004, Gilead updated Viread's EU labeling to change the recommended renal monitoring schedule and recommend that doctors monitor creatinine clearance, which gives a more accurate picture of kidney function, rather than serum creatinine.⁶⁶ Gilead continued to instruct doctors in the EU to monitor TDF patients more carefully than it instructed doctors in the U.S.:

Viread's U.S. Labeling 12/8/2004	Viread's EU Labeling 12/8/2004
<u>Patients at risk</u> for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents <u>should be carefully monitored for changes in serum creatinine and phosphorus.</u>	<u>Monitoring of renal function (creatinine clearance and serum phosphate) is recommended before taking tenofovir disoproxil fumarate, every four weeks during the first year, and then every three months. In patients at risk</u> for, or with a history of, renal dysfunction, and patients with renal insufficiency, <u>consideration should be given to more frequent monitoring of renal function.</u>

224. Like the initial EU label, the 2004 EU label also instructed physicians when to increase monitoring and consider treatment interruption in light of the results of frequent monitoring. Although Gilead instructed U.S. doctors to adjust the dose interval for patients with creatinine clearance <50 mL/min, it did not tell doctors to monitor for creatinine clearance (only serum creatinine for some patients) and only instructed doctors to monitor patients' serum creatinine if they were at risk for, or had a history of, renal impairment:

Viread's U.S. Labeling 12/8/2004	Viread's EU Labeling 12/8/2004
Dosing interval adjustment is recommended in all patients with creatinine clearance <50 mL/min.	If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min, renal function should be re-evaluated within one week and the dose interval of Viread adjusted (see 4.2). Consideration should also be given to interrupting treatment with tenofovir disoproxil fumarate in patients with creatinine

⁶⁶ Gilead did not recommend that doctors monitor creatinine clearance in the U.S. until 2007.

Viread's U.S. Labeling 12/8/2004	Viread's EU Labeling 12/8/2004
	clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).

225. After Gilead began recommending in its U.S. labeling that doctors calculate creatinine clearance in all patients prior to initiating therapy and as clinically appropriate during therapy, Gilead still gave stronger warnings in the EU—recommending that EU doctors monitor all patients' creatinine clearance and serum phosphate every four weeks during the first year, then every three months:

Viread's U.S. Labeling 05/21/2007	Viread's EU Labeling 05/21/2007
It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. <u>Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.</u>	It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with tenofovir disoproxil fumarate and <u>renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year, and then every three months. In patients at risk for renal impairment, consideration should be given to more frequent monitoring of renal function.</u>

226. Gilead instructs in Viread's most recent EU labeling "that renal function (creatinine clearance and serum phosphate) [should be] assessed in all patients prior to initiating therapy with tenofovir disoproxil fumarate and ... also monitored after two to four weeks of treatment, after three months of treatment, and every three to six months thereafter in patients without renal risk factors." For patients at risk for renal impairment, Gilead states that more frequent monitoring of renal function is "required."

227. Gilead has updated its Viread EU labeling multiple times every year since 2002. Each time, Gilead determined that it should instruct doctors in the EU that they should monitor all patients' kidneys on a frequent, specific schedule using multiple markers of kidney function, including serum phosphorus.

228. On February 24, 2005, Truvada received approval to be marketed in the EU. As with Viread, Gilead's Truvada EU labeling contained stronger monitoring warnings than its U.S. labeling at the time of approval:

Truvada's U.S. Labeling 08/02/2004	Truvada's EU Labeling 02/24/2005
<p><u>Patients at risk</u> for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents <u>should be carefully monitored for changes in serum creatinine and phosphorus.</u></p>	<p><u>Careful monitoring of renal function (serum creatinine and serum phosphate) is recommended before taking Truvada, every four weeks during the first year, and then every three months.</u> In patients with a history of renal dysfunction or <u>in patients who are at risk for renal dysfunction, consideration should be given to more frequent monitoring of renal function.</u></p>

229. Like its Viread EU labeling, Gilead's Truvada EU labeling also instructed physicians to increase monitoring and consider treatment interruption if the results of frequent monitoring showed that a patient's serum phosphate or creatinine clearance fell below a specified level. Gilead's U.S. labeling recommended only that patients with creatinine clearance < 50 mL/min receive a dose adjustment—though Gilead did not recommend that doctors monitor patients' creatinine clearance (and would not do so for almost three years) and only instructed doctors to monitor patients' serum creatinine if they were at risk for, or had a history of, renal impairment.

230. In Truvada's most recent SmPC, Gilead continues to instruct doctors as to frequent, routine monitoring of renal function (creatinine clearance and serum phosphate) for patients without preexisting risk factors for renal disease: at treatment initiation and then "after two to four weeks of use, after three months of use and every three to six months thereafter." For patients at risk for renal disease, Gilead warns that more frequent monitoring of renal function is "required."

231. Gilead has updated its Truvada EU labeling multiple times every year since 2005. Each time, Gilead determined that it should instruct doctors in the EU to monitor all patients' kidneys on a frequent, specific schedule using multiple markers of kidney function, including serum phosphorus.

232. In 2006, Gilead issued a "Dear Doctor" letter to physicians in the EU about the importance of frequent, routine monitoring of all TDF patients' renal function. Gilead issued no such letter to doctors in the U.S., though the risk to patients' kidneys was the same.

233. On December 18, 2007, Atripla received approval to be marketed in the EU. As with Viread and Truvada, Gilead's Atripla EU labeling contained stronger monitoring warnings than its U.S. labeling at the time of approval:

Atripla's U.S. Labeling 07/12/2006	Atripla's EU Labeling 12/18/2007
<p><u>Patients at risk</u> for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents <u>should be carefully monitored for changes in serum creatinine and phosphorus.</u></p>	<p><u>It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with Atripla and renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year and then every three months.</u> In patients with a history of renal dysfunction or in <u>patients who are at risk</u> for renal dysfunction, <u>consideration must be given to more frequent monitoring of renal function.</u></p>

234. Like its Viread EU and Truvada EU labeling, Gilead's Atripla EU labeling also instructed physicians to increase monitoring and consider treatment interruption if the results of frequent monitoring showed that a patient's serum phosphate or creatinine clearance fell below a specified level. Gilead's U.S. labeling stated only that patients with creatinine clearance < 50 mL/min should not receive Atripla—though Gilead did not recommend that doctors monitor patients' creatinine clearance (and would not do so for approximately another year) and only instructed doctors to monitor patients' serum creatinine if they were at risk for, or had a history of, renal impairment:

Atripla's U.S. Labeling 07/12/2006	Atripla's EU Labeling 12/18/2007
<p>Since ATRIPLA is a combination product and the dose of the individual components cannot be altered, patients with creatinine clearance <50 mL/min should not receive ATRIPLA.</p>	<p>If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving Atripla, renal function must be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Since Atripla is a combination product and the dosing interval of the individual components cannot be altered, treatment with Atripla must be interrupted in patients with confirmed creatinine clearance < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).</p>

235. In Atripla's most recent SmPC, Gilead instructs doctors that creatinine clearance should be calculated in all patients prior to initiating therapy and renal function (creatinine clearance and serum phosphate) be monitored after two to four weeks of use, after three months of treatment and every three to six months thereafter in patients without renal risk factors. For patients at risk, Gilead states that more frequent monitoring is "required."

236. Gilead has updated its Atripla EU labeling multiple times every year since 2007. Each time, Gilead determined that it should instruct doctors in the EU to monitor all patients' kidneys on a frequent, specific schedule using multiple markers of kidney function, including serum phosphorus.

237. On November 30, 2011, Complera (under the trade name Eviplera) received approval to be marketed in the EU. As with Viread, Truvada, and Atripla, Gilead's Complera EU labeling contained stronger monitoring warnings than its U.S. labeling at the time of approval:

Complera's U.S. Labeling 08/10/2011	Complera's EU Labeling 11/30/11
It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with COMPLERA. <u>Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk</u> for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA.	It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with Eviplera and <u>renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year and then every three months. In patients at risk</u> for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, <u>consideration should be given to more frequent monitoring of renal function.</u>

238. Like its Viread EU, Truvada EU, and Atripla EU labeling, Gilead's Complera EU labeling also instructed physicians to increase monitoring and consider treatment interruption if the results of frequent monitoring showed that a patient's serum phosphate or creatinine clearance fell below a specified level. Gilead's U.S. labeling stated only that patients with creatinine clearance < 50 mL/min should not receive Complera:

Complera's U.S. Labeling 08/10/2011	Complera's EU Labeling 11/30/11
Since COMPLERA is a combination product and the dose of the individual components cannot be altered, patients with creatinine clearance below 50 mL per minute should not receive COMPLERA.	If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving Eviplera, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Since Eviplera is a combination product and the dosing interval of the individual components cannot be altered, treatment with Eviplera must be interrupted in patients with confirmed creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).

239. In Complera’s/Eviplera’s most recent SmPC, Gilead instructs that creatinine clearance should be calculated in all patients prior to initiating therapy and renal function (creatinine clearance and serum phosphate) be monitored after two to four weeks of use, after three months of treatment and every three to six months thereafter in patients without renal risk factors. For patients at risk, Gilead states that more frequent monitoring is “required.”

240. Gilead has updated its Complera EU labeling multiple times every year since 2011. Each time, Gilead determined that it should instruct doctors in the EU to monitor all patients’ kidneys on a frequent, specific schedule using multiple markers of kidney function, including serum phosphorus.

241. On May 27, 2013, Stribild received approval to be marketed in the EU. As with Viread, Truvada, Atripla, and Complera, Gilead included in its Stribild EU labeling stronger monitoring warnings than its U.S. labeling at the time of approval:

Stribild U.S. Labeling 08/27/2012	Stribild’s EU Labeling 05/27/2013
Estimated creatinine clearance, urine glucose and urine protein should be documented in all patients prior to initiating therapy.... <u>Routine monitoring of estimated creatinine clearance, urine glucose, and urine protein should be performed during STRIBILD therapy in all patients. Additionally, serum phosphorus should be measured in patients at risk for renal impairment.</u>	Creatinine clearance should be calculated and urine glucose and urine protein should be determined in all patients ... <u>Creatinine clearance, serum phosphate, urine glucose and urine protein should be monitored every four weeks during the first year and then every three months during Stribild therapy. In patients at risk for renal impairment consideration should be given to more frequent monitoring of renal function.</u>

242. Gilead also included in its Stribild EU labeling a stronger warning about initiating the drug in patients with mild renal impairment:

Stribild U.S. Labeling 08/27/2012	Stribild’s EU Labeling 05/27/2013
STRIBILD should not be initiated in patients with estimated creatinine clearance below 70 mL per min.	Stribild should not be initiated in patients with creatinine clearance < 70 mL/min. <u>It is recommended that Stribild is not initiated in patients with creatinine clearance < 90 mL/min unless, after review of the available treatment options, it is considered that Stribild is the preferred treatment for the individual patient.</u>

1 243. In Stribild’s most recent SmPC, Gilead states that for patients at risk, physician
2 monitoring of creatinine clearance, serum phosphate, urine glucose, and urine protein more frequently
3 than every four weeks during the first year of treatment and then every three months during Stribild
4 therapy is “required.”

5 244. Gilead has updated its Stribild EU labeling multiple times every year since 2013. Each
6 time, Gilead determined that it should instruct doctors in the EU to monitor all patients’ kidneys on a
7 frequent, specific schedule using multiple markers of kidney function, including serum phosphorus.

8 245. Unlike Gilead’s U.S. labeling, Gilead’s EU labeling for Viread and Truvada also
9 discloses that a higher risk of renal impairment has been reported in patients receiving TDF as part of
10 a ritonavir or cobicistat-boosted regimen (like Stribild), and doctors should carefully evaluate whether
11 it is appropriate to prescribe TDF as part of a boosted regimen in patients with renal risk factors.

12 246. There is no medical, clinical, or scientific basis for the differences between the warnings
13 contained in Gilead’s labeling for its TDF-based products in the U.S. and its labeling for the same
14 products in the EU. Gilead knew that it should instruct doctors to monitor all patients for multiple
15 markers of kidney function on a frequent schedule but did not do so in the U.S.

16 247. Gilead was more concerned with increasing or maintaining TDF Drug sales in the U.S.
17 by downplaying the safety risk and the need for careful, frequent monitoring of all patients than it was
18 in safeguarding patients from the known risks of TDF toxicity.

19 248. In addition, until 2018, Gilead’s U.S. warnings about the need to monitor patients for
20 renal effects of Viread, Truvada, Atripla, and Complera were also far weaker than the warnings it gives
21 to monitor patients for renal effects of TAF, even though TAF is far less toxic to kidneys than TDF.
22 Gilead has consistently warned doctors to monitor all patients taking TAF-based drugs for multiple
23 markers of renal function, including urine glucose and urine protein, not just estimated creatinine
24 clearance.

25 249. For example, when the FDA approved Odefsey—the TAF version of Complera—on
26 March 1, 2016, Gilead gave stronger monitoring warnings for safer Odefsey than it did for Complera,
27 telling doctors that they should monitor all Odefsey patients, not just those at risk, for multiple markers
28 of kidney function:

Complera's U.S. Label 03/01/2016	Odefsey's Labeling 03/01/2016
<p><u>It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy</u> with COMPLERA. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA®, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of COMPLERA and periodically during COMPLERA therapy.</p>	<p><u>Estimated creatinine clearance, urine glucose and urine protein should be assessed before initiating ODEFSEY therapy and should be monitored during therapy in all patients.</u> Serum phosphorus should be monitored in patients with chronic kidney disease because these patients are at greater risk of developing Fanconi syndrome on tenofovir prodrugs. Discontinue ODEFSEY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.⁶⁷</p>

250. When the FDA approved Descovy—the TAF version of Truvada—on April 4, 2016, Gilead gave stronger monitoring warnings for safer Descovy than it did for Truvada, telling doctors that they should monitor all Descovy patients, not just those at risk, for multiple markers of kidney function:

Truvada U.S. Labeling 04/04/2016	Descovy U.S. Labeling 04/04/2016
<p>It is recommended that <u>estimated creatinine clearance be assessed in all individuals prior to initiating therapy and as clinically appropriate during therapy</u> with TRUVADA. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA®, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of TRUVADA, and periodically during TRUVADA therapy.</p>	<p><u>Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating DESCOVY therapy and should be monitored during therapy in all patients.</u> Serum phosphorus should be monitored in patients with chronic kidney disease because these patients are at greater risk of developing Fanconi syndrome on tenofovir prodrugs. Discontinue DESCOVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.</p>

251. Gilead determined that it should give stronger monitoring warnings for its safer TAF-based drugs, yet failed to strengthen its TDF Drug warnings for years.

2. Gilead failed to adequately warn patients about the risks of TDF.

252. Gilead failed to adequately warn patients about the risks of TDF, and the need to routinely monitor all patients taking TDF, in direct-to-consumer advertising and in patient labeling.

⁶⁷ On August 17, 2017, Gilead updated its Odefsey label to tell doctors to all monitor all patients, not just those with chronic kidney disease, for serum phosphorus.

1 253. Gilead promoted its TDF Drugs directly to patients through direct-to-consumer
2 advertising, including print and online media. Like its sales force’s promotion to doctors, Gilead’s
3 consumer advertising downplayed the risks of TDF toxicity by, among other things, hiding risk
4 information relative to the benefits of the drugs, and suggesting that kidney and bone adverse events
5 only occurred in, and monitoring was only necessary for, patients with risk factors for such injuries.

6 254. For example, a print advertisement for Truvada that appeared in the November 2004
7 edition of *The Advocate*, the oldest and largest lesbian, gay, bisexual, and transgender magazine in the
8 U.S., stated under the heading “Important Safety Information” that: “If you have had kidney problems
9 or take other medicines that can cause kidney problems, your medical professional should do regular
10 blood tests to check your kidneys.” Yet Gilead knew by this time that adverse kidney events were not
11 limited to at risk patients, and thus should have warned doctors and patients about the need for frequent
12 monitoring of all patients.

13 255. On March 26, 2010, the FDA issued another Warning Letter to Gilead, this time in
14 connection with Gilead’s direct-to-consumer print advertising for Truvada. The FDA stated that
15 Gilead’s Truvada advertisement was false and misleading because it overstated the efficacy of Truvada
16 and minimized the risks associated with the drug, in violation of the Federal Food, Drug, and Cosmetic
17 Act and FDA implementing regulations. The FDA noted that Truvada is associated with “serious risks”
18 like new onset or worsening renal impairment, including cases of acute renal failure and Fanconi
19 syndrome (renal tubular injury with severe hypophosphatemia), and decreases in bone mineral density,
20 including cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute
21 to fractures). The agency stated that Gilead’s Truvada advertising was false or misleading because it
22 failed to present the risks associated with Truvada with a prominence and readability comparable to
23 the statements regarding the drug’s benefits.

24 256. In addition to the reasons set forth in the Warning Letter, the Truvada advertising was
25 also false and misleading because, like the earlier Truvada advertising, it continued to suggest that
26 kidney problems only occurred in, and monitoring was also necessary for, patients that had had kidney
27 problems in the past or took other medications that can cause kidney problems.

1 257. Upon information and belief, Gilead’s other direct-to-consumer advertising for Viread,
2 Truvada, Atripla, and Complera similarly failed to adequately warn patients about the true risk of TDF
3 and the need to routinely monitor all patients for TDF-associated kidney and bone effects.

4 258. Gilead’s patient package inserts for Viread, Truvada, Atripla, and Complera also failed
5 to warn about all patients’ need to be routinely monitored by their doctors for adverse kidney and bone
6 effects. The patient package inserts said nothing for years about monitoring anyone other those who
7 were already at risk for kidney and bone problems despite Gilead’s knowledge that TDF was injuring
8 patients without identified risk factors for such injuries.

9 259. Gilead’s patient package inserts for Viread, Truvada, Atripla, and Complera failed to
10 adequately warn patients even after Gilead had inadequately updated the warnings in its prescriber
11 labeling.

12 260. For example, Gilead did not disclose to patients that Viread may cause “new or worse
13 kidney problems” until more than two years after Gilead added that warning to the Viread prescriber
14 labeling. And Gilead waited many more years before it added the “new or worse kidney problems”
15 disclosure to the patient package inserts for other TDF products; it did not appear in the Truvada patient
16 package insert until June 17, 2013 and did not appear in the Atripla patient package insert until July
17 25, 2018—nearly five and ten years respectively after Gilead first warned doctors that TDF may cause
18 “new onset or worsening renal impairment.”

19 261. Gilead similarly delayed disclosing to patients in the patient package inserts about
20 doctors’ need to assess all plaintiffs’ kidney function prior to initiating treatment with TDF. Although
21 Gilead added that warning to the Viread prescriber labeling in May 2007, it did not tell patients that
22 “[y]our healthcare provider should do blood tests to check your kidneys before you start treatment”
23 with TDF until August 16, 2012, for Viread, May 15, 2018, for Truvada, July 25, 2018, for Atripla,
24 and January 25, 2013, for Complera. At a minimum, Gilead was grossly negligent in failing to ensure
25 that its warnings to patients were consistent with those it gave to doctors and the patient warnings it
26 gave were consistent among its various TDF Drugs.

1 **3. Gilead could have unilaterally strengthened its TDF drug labels.**

2 262. Gilead could have strengthened the Warnings, Precautions, and Adverse Events
3 sections of the labels for its TDF Drugs unilaterally without prior FDA approval.

4 **a. Gilead could have unilaterally strengthened its warnings before FDA**
5 **approval.**

6 263. Each time Gilead sought FDA approval for a new TDF Drug, it could have strengthened
7 its label before the drug obtained FDA approval. Gilead bears primary responsibility for its drug
8 labeling at all times, and was responsible for crafting adequate labels before the drugs were FDA
9 approved. No federal law prevented Gilead from submitting a stronger warning label to the FDA prior
10 to the initial approval of the TDF Drugs. And the FDA would not have prevented Gilead from
11 strengthening its monitoring warnings in advance of FDA approval.

12 264. Gilead's initial EU label for its first TDF Drug, Viread, included stronger monitoring
13 warnings. As it did in the EU, Gilead could have included stronger warnings in its initial Viread label
14 in the U.S.—had Gilead been concerned with patient safety rather than U.S. sales.

15 265. Moreover, before Gilead submitted Truvada, Atripla, Complera, and Stribild for FDA
16 approval in the U.S., it knew that it gave stronger monitoring warnings for its TDF Drugs in the EU.
17 Gilead knew, as evidenced by its EU labels, that stronger warnings were warranted. It could have and
18 should have used this knowledge to strengthen its U.S. labels.

19 266. In addition, once TDF was on the market, each time Gilead submitted a new TDF Drug
20 for FDA approval, it did so with years of cumulative knowledge as to the adverse toxic effects of TDF.
21 Faced with accumulating information about adverse kidney and bone toxicity, including in patients
22 without preexisting risk factors, Gilead could have strengthened its monitoring warnings before
23 submitting the drugs for FDA approval.

24 267. The FDA would not have rejected Gilead's stronger warnings. The FDA has, in fact,
25 approved labels including stronger monitoring warnings for the TDF Drugs, as well as the safer TAF
26 drugs.

1 **b. Gilead could have unilaterally strengthened its warnings after FDA**
2 **approval.**

3 **(1) Before August 22, 2008**

4 268. Prior to August 22, 2008, Gilead could have strengthened its Viread, Truvada, and
5 Atripla labels via CBE without prior FDA approval. Under the CBE regulation in effect during that
6 time, Gilead could have simply submitted a supplemental submission strengthening the labels'
7 warnings and/or its instructions about the safe administration of the drugs. 21 C.F.R.
8 § 314.70(c)(6)(iii).

9 269. Among other things, Gilead could have strengthened the labels' warnings by providing
10 additional information about laboratory tests helpful in following the patient's response or identifying
11 possible adverse reactions, including such factors as the range of normal and abnormal values and the
12 recommended frequency with which tests should be performed before, during, and after therapy. 21
13 C.F.R. § 201.57(c)(6).

14 270. Prior to August 22, 2008, Gilead could have strengthened its labels via CBE without
15 regard to whether it possessed information that it did not previously provide to the FDA.

16 271. The FDA would not have rejected Gilead's supplemental submission to strengthen the
17 TDF labels. The FDA has, in fact, approved labels including stronger monitoring warnings for the
18 TDF Drugs, as well as the safer TAF drugs.

19 **(2) On and after August 22, 2008, through July 2012**

20 272. On and after August 22, 2008, when the CBE regulation was amended, Gilead could
21 have unilaterally strengthened its labels for Viread, Truvada, Atripla, and Complera post-FDA
22 approval based on "newly acquired information," *i.e.*, information that was not previously presented
23 to the FDA.

24 273. Gilead could have strengthened the Warnings, Precautions, and Adverse Events
25 sections of its labels unilaterally, without requiring prior FDA approval, based on, among other things:
26 increasing post-approval evidence that patients with and without preexisting risk factors were
27 experiencing kidney and bone adverse effects with a frequency greater than reported in Gilead's
28 clinical trials; expanding post-approval evidence that all patients are at risk for TDF-induced

1 nephrotoxicity, meaning that doctors should monitor all patients for multiple indicators of renal
2 function, including tubular dysfunction; and Gilead’s own post-approval determinations to give
3 stronger warnings regarding the exact same TDF Drugs in the EU.

4 274. Except for Stribild, Gilead’s clinical trials of the TDF Drugs, upon which FDA approval
5 was based, did not show significant nephrotoxicity of TDF, despite preclinical evidence demonstrating
6 that TDF could be highly toxic to kidneys and bones. However, once Gilead started marketing TDF,
7 patients quickly began experiencing TDF’s nephrotoxic effects, some severe and irreversible.
8 Although the FDA became aware, after the clinical trials through adverse event reporting, that TDF
9 was injuring patients’ kidneys and bones, it did not know the true frequency or severity of adverse
10 events, injury, or risk associated with TDF.

11 275. On May 21, 2007, Gilead changed its Viread label to instruct doctors to calculate
12 creatinine clearance in all patients before initiating treatment with TDF and as clinically appropriate
13 during therapy. Gilead recommended the monitoring of creatinine clearance and serum phosphorus
14 only for patients at risk of renal impairment.

15 276. This warning remained inadequate because it failed to instruct doctors to frequently
16 monitor all patients for sufficiently sensitive markers of kidney function that could detect early signs
17 of nephrotoxicity and thus prevent or lessen the harm of TDF. As Gilead had known since at least
18 2002, TDF was injuring patients with no preexisting risk factors for kidney impairment. Gilead’s May
19 21, 2007 label change perpetuated the false distinction between patients “at risk” for TDF-induced
20 nephrotoxicity and everyone else. But as subsequent studies would make clear, while there may be
21 certain factors that increase a patient’s risk of TDF-induced renal damage, *all TDF patients are at*
22 *risk*—making frequent, careful monitoring of all patients essential for safe use of the drug.

23 277. As clinicians’ experience with TDF grew, the medical literature recognized that even if
24 TDF may not frequently impair kidneys’ *glomerular function*—as measured by serum creatinine or
25 creatinine clearance—in the absence of established risk factors, TDF-induced damage to kidneys’
26 *tubular function* is much more common and cannot be adequately predicted by traditional risk factors
27 for kidney impairment or detected by monitoring for glomerular function. These new studies
28 demonstrated a heightened risk to all patients, leading study authors to conclude that all patients must

1 be frequently monitored for markers of tubular function—e.g., serum phosphorus, in addition to
2 creatinine clearance.

3 278. For example, the 2009 paper, Labarga P., *et al.*, “Kidney tubular abnormalities in the
4 absence of impaired glomerular function in HIV patients treated with tenofovir,” described the study
5 of glomerular and tubular function in 284 patients, 154 of whom took TDF, 49 of whom took another
6 HIV regimen, and 81 of whom took no antiretroviral drugs. The authors found that glomerular
7 function, as measured by plasma creatinine levels or creatinine clearance or both, was within normal
8 limits and comparable among all study groups. Tubular dysfunction, on the other hand, was far more
9 frequent in the TDF group (22%), as compared to those never treated with TDF (6%) or never exposed
10 to antiretrovirals (12%). The authors also identified three TDF patients with complete Fanconi
11 syndrome (the signature TDF toxicity), even though each patient’s creatinine clearance was within the
12 normal range. After follow-up, the data showed that the TDF patients had a significantly greater risk
13 for tubular damage than patients never treated with TDF: an estimated 25% rate of tubular dysfunction
14 at 4 years for TDF patients compared to null for the rest.

15 279. The Labarga study also found that no risk factor other than TDF use and old age was
16 predictive of tubular dysfunction. And because estimates of glomerular function like creatinine
17 clearance were not predictive of tubular function, the authors explained that unless tubular parameters
18 like urine glucose and/or phosphorus are routinely monitored, tubular abnormalities may go
19 undiagnosed. And if tubular damage persists unnoticed, patients may progress to more severe kidney
20 damage and experience a chronic loss of phosphorus, leading to bone mineral density loss and
21 premature osteoporosis. The authors recommended that all TDF patients be monitored for signs of
22 tubular damage so that a switch in therapy could be considered in the event of progressive
23 deterioration.

24 280. A 2011 article, Hall AM *et al.*, “Tenofovir-associated kidney toxicity in HIV-infected
25 patients: a review of the evidence,” conducted a literature review and further addressed the disconnect
26 between results of studies examining markers of glomerular function with the nephrotoxicity seen in
27 practice. The authors noted that prior studies tended to establish that TDF was not often significantly
28 toxic to the glomerulus—which contrasted with the authors’ clinical experience in treating TDF

1 patients for nephrotoxicity. In practice, TDF-associated nephrotoxicity was the authors' most common
2 reason for referral of HIV patients to specialist renal services. The authors explained that the main site
3 of TDF toxicity was the proximal renal tubule (not the glomerulus) and that proximal tubule
4 dysfunction may not be detected by measuring glomerular filtration.

5 281. Because (a) TDF-associated nephrotoxicity can occur in patients without obvious risks
6 factors and at highly variable times after the initiation of therapy, and (b) standard tests of glomerular
7 function are insufficiently sensitive to detect early or mild cases of nephrotoxicity, the authors
8 concluded that all patients on TDF should be carefully and routinely monitored (every 3 months during
9 the first year then twice yearly) for signs of both glomerular and tubular dysfunction so that long-term
10 effects on kidney and bone health can be assessed.

11 282. A 2012 paper, Scherzer, R., *et al.*, "Association of Tenofovir Exposure with Kidney
12 Disease Risk in HIV Infection," discussed the authors' study of 10,841 HIV-infected patients from the
13 Veterans Health Administration to assess the associations of tenofovir with kidney disease outcomes.
14 The authors found that each year of tenofovir exposure was associated with a 34% increased risk of
15 proteinuria, 11% increased risk of rapid decline in kidney function, and 33% increased risk of chronic
16 kidney disease. The results provided "strong evidence that tenofovir may cause clinically significant
17 toxicity to the kidney that is not reversible." The study also demonstrated that traditional risk factors
18 did not worsen the effects of tenofovir. The authors concluded that "while traditional risk factors such
19 as hypertension, older age, and diabetes may increase the risk for kidney disease, tenofovir is
20 associated with elevated risk even in patients without preexisting risk factors."⁶⁸

21 283. The authors explained the strength of their results in light of the study's large patient
22 population and inclusion of patients who are often excluded from clinical trials or do not qualify or
23 volunteer for cohort studies. The authors contrasted their study with the design of previous studies
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25

26 ⁶⁸ The FDA cited the Scherzer study in connection with its medical review of the Stribild NDA in
27 July 2012. At most, this demonstrates the FDA's knowledge of this study as of July 2012—
28 approximately 4 years after the CBE regulation requiring "newly acquired information" became
effective. Plaintiffs do not assert post-FDA approval failure to warn claims with respect to Stribild.

1 which made them less able to detect statistically significant associations between tenofovir use and
2 kidney disease.

3 284. A 2013 paper, Reynes, J., *et al.*, “Tubular and glomerular proteinuria in HIV-infected
4 adults with estimated glomerular filtration rate ≥ 60 ml/min per 1.73,” recommended that all TDF
5 patients be systematically monitored for markers of tubular injury in light of the authors’ finding that
6 nearly 20% of 1200 patients had proteinuria even though they had a normal creatinine-based estimated
7 glomerular filtration rate.

8 285. And a 2014 paper, Bonjoch, A., *et al.*, “High prevalence of signs of renal damage
9 despite normal renal function in a cohort of HIV-infected patients: evaluation of associated factors,”
10 also found that signs of renal damage were “highly frequent” even in patients with a normal estimated
11 glomerular filtration rate. The authors concluded that the data demonstrated the need for early
12 detection of renal injury, even in patients with normal renal function.

13 286. These papers, and others in this timeframe that demonstrated a high percentage of TDF
14 patients with proximal renal tubular dysfunction, stand in stark contrast to Gilead’s Viread clinical
15 trials and subsequent attempts to maintain that only some TDF patients are at risk. Unlike the Viread
16 clinical trials, these papers showed significant nephrotoxicity of TDF—with toxicity occurring at a
17 high frequency and high risks of kidney disease outcomes looming even in patients with normal
18 glomerular function and without traditional risk factors.

19 287. The clinical trials reported that the frequency of renal events leading to drug
20 discontinuation was low (0.4%). Despite these results, Gilead knew that the potential for TDF to be
21 toxic was high, particularly in real world settings over the long-term. And, indeed, multiple
22 retrospective studies have demonstrated that the rate of renal adverse events leading to drug
23 discontinuation was many times higher than what was reported in clinical trials. For example, the 2011
24 paper, “Tenofovir-induced renal toxicity in 324 HIV-infected antiretroviral-naïve patients,” found that
25 drug discontinuation due to decline in GFR or tubular dysfunction was 9.2%.

26 288. Postmarketing adverse event reports did not put the FDA on notice of the frequency or
27 severity of the risk. Adverse event reports underreport the true incidence of adverse events because
28 they are based on voluntary reporting. And they do not reflect the damage TDF inflicts on kidneys and

1 bones before renal function declines, the risk of future adverse kidney or bone outcomes, nor the
2 benefits of frequent, careful monitoring of all patients for early signs of nephrotoxicity as demonstrated
3 by these new studies.

4 289. Further, there is no evidence that Gilead submitted to the FDA analyses demonstrating
5 that TDF patients have a high frequency of renal damage or the true extent of the risk nephrotoxicity
6 poses to all TDF patients even if they have normal glomerular function or do not have preexisting risk
7 factors.

8 290. Gilead did not submit analyses to the FDA establishing the full extent of the frequency
9 or severity of risk that TDF poses to all patients, nor did it tell the FDA that the one marker of kidney
10 function Gilead was warning doctors to monitor in all patients after May 21, 2007 could not adequately
11 detect the type of kidney injury that was frequently occurring in all TDF patients (and, which left
12 unchecked, would cause more severe kidney injury and also harm patients' bones). Gilead could have
13 analyzed the accumulating data demonstrating the higher frequency and severity of the risk to all TDF
14 patients and strengthened its warnings, but did not.

15 291. Until the FDA's review of the Stribild NDA in 2012, there is no evidence that the
16 agency reviewed any medical literature regarding TDF or other analyses describing how post-approval
17 renal and bone injury and/or adverse events were occurring at a frequency or severity much greater
18 than that reported in the registrational clinical trials. The FDA based its approval of Viread on the
19 preclinical data and clinical trials Gilead submitted in its Viread NDA. After Viread was approved, the
20 FDA based its approvals of the Truvada, Atripla, and Complera NDAs on Gilead's data showing the
21 bioequivalence of those combination drugs to their individual components. The FDA's approvals of
22 Truvada, Atripla, and Complera were not based on any new clinical studies or other analyses regarding
23 safety of TDF. When the FDA conducted a more searching review in connection with the Stribild
24 NDA, Gilead proposed and the FDA approved stronger monitoring warnings for Stribild, which
25 included recommending the monitoring of all patients for glomerular and tubular injury.

26 292. Unlike in the U.S., Gilead did warn—since 2002—physicians in the EU to frequently
27 monitor all patients for both glomerular (creatinine clearance) and tubular (serum phosphorus) injury.
28 In fact, after Gilead received FDA approval to market each of the TDF Drugs, it repeatedly determined

1 to give stronger monitoring warnings for the exact same TDF Drugs in the EU. Upon information and
2 belief, Gilead did not disclose to the FDA that it gave stronger monitoring warnings in the EU for the
3 exact same products nor did it disclose its scientific or medical reasons for doing so.

4 293. In addition, once Gilead finally launched the safer TAF-based drugs (after approval of
5 the TDF Drugs) it also gave stronger monitoring warnings for the safer TAF drugs than it gave in the
6 TDF Drugs' labels, including recommending that doctors monitor all patients for both glomerular and
7 tubular injury.

8 294. The FDA would not have rejected a label change strengthening monitoring
9 recommendations to protect all patients from risks of TDF-induced kidney and bone adverse effects.
10 In 2018, the FDA did, in fact, approve labels including stronger monitoring warnings for Viread,
11 Truvada, Atripla, and Complera, like it did for the safer TAF drugs years earlier.

12 VI. TOLLING OF THE STATUTE OF LIMITATIONS

13 295. Gilead misrepresented that TAF was "new" despite knowing that it had discovered the
14 benefits of TAF even before Viread was approved in 2001.

15 296. Gilead misrepresented the reasons that it shelved TAF in 2004, asserting that TAF could
16 not be differentiated from TDF when it knew that TAF was, in fact, highly differentiated from TDF.

17 297. Gilead concealed that it shelved TAF in 2004 in order to extend the lifecycle of its HIV
18 product portfolio while patients were injured by TDF-induced kidney and bone toxicity.

19 298. Gilead misrepresented that it renewed development of TAF because of the needs of an
20 aging HIV population. Gilead knew by 2004 when it halted TAF development that, as a result of cART,
21 many HIV patients had a normal life expectancy.

22 299. For years, Gilead has publicized the pretext for its decision to halt and then renew TAF
23 development in order to conceal the existence of Plaintiffs' claims.

24 300. Gilead concealed that it did not reduce the dose of TDF in Stribild even though it knew
25 to reduce the tenofovir prodrug dose when combined with cobicistat.

26 301. Gilead concealed the true risk of kidney and bone injuries TDF posed to patients who
27 did not have preexisting risk factors for such injuries and concealed from U.S. doctors and patients
28 what it knew about the need to monitor all patients for TDF associated toxicity.

1 302. Because of Gilead’s misrepresentations and omissions, plaintiffs did not know and had
2 no reason to suspect that Gilead’s wrongdoing was the cause of their injuries and could not have
3 discovered their claims.

4 303. No reasonable person taking TDF-based drugs and experiencing kidney and bone
5 toxicities would have suspected that Gilead purposefully withheld a safer design that would have
6 ameliorated those very side effects.

7 304. No reasonable person without prior risk factors for renal or bone harm taking TDF-
8 based drugs and experiencing kidney and bone toxicities would have suspected that Gilead failed to
9 adequately warn them because the label misleadingly suggests that only patients with preexisting risk
10 factors were in danger.

11 305. No reasonable person would have suspected that Gilead provided stronger warnings to
12 patients and doctors in the EU than it did in the U.S. for the exact same TDF products.

13 306. Gilead’s misrepresentations and omissions would lead a reasonable person to believe
14 that he or she did not have a claim for relief.

15 307. Because of Gilead’s misrepresentations and omissions, neither Plaintiffs nor any
16 reasonable person would have had reason to conduct an investigation. Once Plaintiffs suspected that
17 Gilead’s wrongdoing was the cause of their injuries, they were diligent in trying to uncover the facts.

18 308. Gilead’s misrepresentations and omissions regarding its refusal to earlier market TAF-
19 designed products and the true risks of TDF constitute continuing wrongs that continue to this day.

20 **VII. CLAIMS FOR RELIEF⁶⁹**

21 **COUNT I**

22 **STRICT PRODUCTS LIABILITY – DESIGN DEFECT**
23 **UNDER THE LAWS OF THE STATES OF ALABAMA,⁷⁰ GEORGIA, NEVADA, AND**
24 **TEXAS**

25 309. Plaintiffs reallege and incorporate the allegations made above as if fully set forth below.

26 ⁶⁹ Plaintiffs assert claims under the laws of the states in which they reside or ingested the relevant
27 TDF Drugs.

28 ⁷⁰ The Alabama Plaintiffs assert their claims under the judicially-created Alabama Extended
Manufacturer’s Liability Doctrine (“AEMLD”).

1 310. Plaintiffs assert pre-approval design defect claims.

2 311. Gilead is the manufacturer and seller of the TDF Drugs.

3 312. The TDF Drugs reached Plaintiffs without substantial change to the condition in which
4 they were sold.

5 313. The TDF Drugs are unreasonably dangerous and unsafe for their intended purpose
6 because they include TDF, which causes kidney and bone toxicity, as the design for delivering
7 tenofovir to the body. The design defect existed in these products at the time they left Gilead's
8 possession.

9 314. Stribild is also unreasonably dangerous and unsafe for its intended purpose because it
10 combines 300 mg TDF with cobicistat, which enhances TDF toxicity. The design defects existed in
11 Stribild at the time it left Gilead's possession.

12 315. The TDF Drugs are not as safe as current technology could make them, nor were they
13 as safe as then-current technology could make them when Gilead first manufactured and distributed
14 each of the TDF Drugs.

15 316. The TDF Drugs were not incapable of being made safe at the time of manufacture and
16 distribution. Gilead knew, before it manufactured and distributed each of the TDF Drugs, that TAF
17 was more potent than TDF and reduced the risk of kidney and bone toxicity compared to TDF. Gilead
18 also knew that it could reduce the dose of TDF in Stribild and achieve the same antiviral response with
19 less kidney and bone toxicity. The TDF Drugs are therefore not unavoidably unsafe.

20 317. The risks of patient harm associated with TDF-induced kidney and bone toxicity were
21 both known to and foreseeable to Gilead.

22 318. Gilead could have reduced or prevented the foreseeable risks of harm associated with
23 TDF by adopting a reasonable and feasible alternative design before FDA approval. Gilead could have
24 incorporated the safer TAF design, which it knew reduces the risks of kidney and bone toxicity and is
25 safer than TDF, into the TDF Drugs before they were approved by the FDA. Gilead did utilize the
26 TAF design instead of TDF in other FDA-approved products that are identical to the TDF Drugs except
27 for the substitution of TAF for TDF. Gilead markets its TAF-designed products as safer than the TDF
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1 Drugs and advocates that doctors switch their patients from a TDF-designed to a TAF-designed
2 product because of TAF's superior safety profile with respect to kidney and bone toxicity.

3 319. A drug product containing TAF could have and would have been FDA approved and
4 on the market years earlier if Gilead had not purposefully shelved the TAF design for approximately
5 six years in order to make more money.

6 320. Gilead could have reduced or prevented the foreseeable risks of harm associated with
7 Stribild by adopting another reasonable and feasible alternative design before FDA approval. Gilead
8 could have reduced the dose of TDF in Stribild before it was approved by the FDA because, as it knew
9 for years, tenofovir concentrations rise significantly when tenofovir is combined with a boosting agent
10 like cobicistat. The reasonableness and feasibility of this alternative design is demonstrated by, *inter*
11 *alia*, the fact that Gilead reduced the dose of the tenofovir prodrug TAF in Genvoya, which is identical
12 to Stribild except for the substitution of TAF for TDF.

13 321. The likelihood and severity of the kidney and bone injuries suffered by patients like
14 Plaintiffs far outweighed Gilead's burden in taking safety measures to reduce or avoid the harm. Given
15 the sheer number of people taking the TDF Drugs, including over the long-term, there was a high
16 likelihood that TDF would injure a very large number of patients, and that a significant number of
17 those injuries would be irreversible. Gilead's burden was small. Gilead had already discovered the
18 safer TAF method of introducing tenofovir into the body before it sought FDA approval for each of
19 the TDF Drugs and using the TAF design would have no adverse impact on the utility of the products.

20 322. TAF-based alternative designs, and a reduced TDF dose design of Stribild, would have
21 accomplished the product's purpose at lesser risk. This is how Gilead markets its TAF-designed
22 products today—as equally or more effective than the TDF Drugs with a reduced risk of kidney and
23 bone toxicity.

24 323. Gilead knew that ordinary patients would use the TDF Drugs without knowledge of the
25 hazards involved in such use. The TDF Drugs failed to perform as an ordinary consumer would expect.

26 324. Gilead knowingly designed its TDF Drugs with TDF rather than safer TAF to maximize
27 profits on its portfolio of TDF profits and extend the lifecycle of its HIV franchise, which formed the
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1 backbone of Gilead's operations. Gilead withheld its safer TAF design to make more money at the
2 expense of patients' health.

3 325. The benefit in promoting enhanced accountability through strict products liability
4 outweighs the benefit of a product that Gilead should have and could have made safer years earlier.

5 326. Plaintiffs ingested one or more of the TDF Drugs for an approved purpose and
6 experienced bone and/or kidney injuries while taking TDF.

7 327. Plaintiffs' bone and kidney toxicity-related injuries were directly and proximately
8 caused by TDF while Plaintiffs used the TDF Drugs in a reasonably foreseeable manner.

9 **COUNT II**

10 **STRICT PRODUCTS LIABILITY – FAILURE TO WARN**
11 **UNDER THE LAWS OF THE STATES OF ALABAMA, GEORGIA, AND NEVADA**

12 328. Plaintiffs reallege and incorporate the allegations made above as if fully set forth below.

13 329. Plaintiffs allege failure to warn claims based on Gilead's ability to strengthen its U.S.
14 labels before FDA approval for all TDF Drugs and after FDA approval for Viread, Truvada, Atripla,
15 and Complera through July 2012.

16 330. Gilead is the manufacturer and seller of the TDF Drugs.

17 331. Gilead was aware of the risks TDF posed to patients' kidneys and bones, and the risks
18 TDF posed to patients' kidneys and bones were knowable, at the time Gilead manufactured, sold, or
19 distributed the TDF Drugs.

20 332. The risks TDF posed to patients' kidneys and bones were known or knowable in light
21 of the scientific and medical knowledge available at the time of manufacture and distribution.

22 333. The need to frequently monitor all TDF patients for kidney toxicity using more than
23 one insufficient marker of kidney function to ensure the safe use of TDF was known or knowable in
24 light of the scientific and medical knowledge available at the time of manufacture and distribution of
25 the TDF Drugs.

26 334. TDF posed a substantial danger to patients' kidneys and bones.

27 335. Ordinary consumers and physicians would not have recognized the potential risks TDF
28 posed to patients' kidneys and bones.

1 336. Gilead failed to adequately warn Plaintiffs and Plaintiffs’ physicians about the risks
2 TDF posed to patients’ kidneys and bones, and the proper and safe use of the TDF Drugs.

3 337. The inadequate warnings and instructions Gilead did provide were minimized, eroded,
4 and nullified by Gilead’s improper promotion of the TDF Drugs to doctors.

5 338. Gilead failed to adequately warn Plaintiffs and Plaintiffs’ physicians that all TDF
6 patients needed to be monitored frequently, on a specific schedule, for TDF-associated toxicity.

7 339. Gilead failed to adequately warn Plaintiffs and Plaintiffs’ physicians that all TDF
8 patients’ kidney function needs to be monitored by measuring more than one insufficient marker of
9 kidney function.

10 340. Plaintiffs were injured by using TDF in a reasonably foreseeable way.

11 341. The lack of adequate warnings and instructions was a substantial factor in causing
12 Plaintiffs’ injuries.

13 342. Had Gilead adequately warned and instructed Plaintiffs, Plaintiffs would have taken the
14 TDF Drugs in a safer way.

15 343. Had Gilead adequately warned and instructed Plaintiffs’ doctors, Plaintiffs’ doctors
16 would have read and heeded such adequate warnings and instructions.

17 344. Plaintiffs’ properly warned physicians would have monitored Plaintiffs differently—by
18 frequently monitoring Plaintiffs using sufficiently sensitive markers of kidney function that would
19 have alerted doctors to early signs of nephrotoxicity, including tubular damage that leads to more
20 severe renal adverse events and bone mineral density loss. Once they recognized the signs of
21 nephrotoxicity, Plaintiffs’ physicians would have taken further action after weighing their treatment
22 options, such as increased monitoring, less frequent dosing, or drug discontinuation, before the damage
23 manifested, worsened, or became irreversible. Plaintiffs’ properly warned physicians would have
24 detected TDF toxicity earlier, thus preventing or lessening Plaintiffs’ injuries.

25 345. Plaintiffs’ bone and kidney toxicity-related injuries were directly and proximately
26 caused by Gilead’s inadequate warnings.

COUNT III

**CONNECTICUT PRODUCTS LIABILITY ACT, CONN.
GEN. STAT. 52-572N ET SEQ.**

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346. Connecticut Plaintiffs reallege and incorporate the allegations made above as if fully set forth below, including but not limited to the allegations specifically contained in the paragraphs corresponding to Counts I and II above.

347. Gilead sold or otherwise put the TDF Drugs into the stream of commerce in a defective condition unreasonably dangerous to ordinary users and consumers like Plaintiffs.

348. The TDF Drugs are defective in design and Gilead failed to adequately warn about the dangers and proper use of the products.

349. Connecticut Plaintiffs are in the class of persons who are ordinary consumers who purchased the products, with the ordinary knowledge common to the community about the products' characteristics.

350. Gilead is in the business of selling pharmaceuticals like the TDF Drugs.

351. The TDF Drugs were expected to, and did, reach users and consumers like Plaintiffs without substantial alteration in the condition in which Gilead sold them.

352. At the time the TDF Drugs left Gilead's control, the TDF Drugs were in a defective condition not contemplated by reasonable persons among those considered expected users or consumers of the products and that will be unreasonably dangerous to the expected, ultimate user or consumer when used in reasonably expected ways of handling or consumption. The TDF Drugs are dangerous to an extent beyond which would be contemplated by the ordinary user and consumer, with ordinary knowledge common to the community as to the product's characteristics.

353. The defective condition of the TDF drugs rendered the products unreasonably dangerous to ultimate users and consumers like Connecticut Plaintiffs.

354. The TDF Drugs are defective because Gilead failed to properly and adequately label the products to give reasonable warnings of the danger about the products or give reasonably complete instructions on proper use of the product. If such warnings were provided, the harm would have been avoided.

1 355. Gilead failed to exercise reasonable care under the circumstances in designing the TDF
2 Drugs and in providing warnings or instructions regarding the dangerous propensities of the TDF
3 Drugs.

4 356. At the time the TDF Drugs left Gilead's control, the risks of the TDF-induced kidney
5 and bone toxicity were known or reasonably foreseeable to Gilead.

6 357. At the time the TDF Drugs left Gilead's control, the inherent, foreseeable and known
7 risks associated with the design exceeded the benefits of the design.

8 358. The defective and unreasonably dangerous condition of the TDF Drugs proximately
9 caused Connecticut Plaintiffs physical injuries to their kidneys and/or bones and damages for which
10 recovery is sought.

11 359. Gilead acted with reckless disregard for the rights and safety of Plaintiffs and acted with
12 intentional and wanton violation of those rights. Plaintiffs seeks punitive damages for injuries caused
13 by Gilead's wanton and malicious conduct.

14 **COUNT IV**

15 **NEGLIGENCE AND GROSS NEGLIGENCE**
16 **UNDER THE LAWS OF THE STATES OF ALABAMA, GEORGIA, NEVADA,**
PENNSYLVANIA, TEXAS, AND VIRGINIA

17 360. Plaintiffs reallege and incorporate the allegations made above as if fully set forth below.

18 361. Gilead has a duty to exercise ordinary care in the design, manufacture, marketing, and
19 sale of its pharmaceutical products, including the TDF Drugs.

20 362. Gilead has a duty to refrain from selling unreasonably dangerous products, including
21 the duty to ensure that its pharmaceutical products do not cause patients to suffer from foreseeable
22 risks of harm.

23 363. Gilead has a duty to monitor the adverse effects associated with its pharmaceutical
24 products, including the TDF Drugs.

25 364. Gilead has a continuing duty to warn of the adverse effects associated with its
26 pharmaceutical products, including the TDF Drugs, to avoid reasonably foreseeable risks.

27 365. Gilead has a duty to identify any laboratory tests helpful in identifying adverse reactions
28 and the recommended frequency with which such tests should be performed.

1 366. Gilead has a duty to exercise reasonable care when it undertakes affirmative acts for
2 the protection of others.

3 367. Gilead owes these duties to Plaintiffs because it was foreseeable to Gilead that patients
4 like Plaintiffs would ingest and consequently be endangered by its TDF Drugs.

5 368. Gilead knew that the TDF design it incorporated into the TDF Drugs was associated
6 with risks of kidney and bone toxicity and caused injuries that resulted from kidney and bone toxicity—
7 including in patients not otherwise at risk for such injuries. Gilead’s knowledge that TDF harmed
8 patients’ kidneys and bones only grew with each year TDF was on the market. By the time Stribild
9 entered the market, Gilead had more than a decade’s worth of knowledge that TDF was toxic to kidneys
10 and bones.

11 369. Gilead knew that combining 300 mg of TDF with cobicistat resulted in even greater
12 toxicity, and that it could reduce the tenofovir prodrug dose when combined with cobicistat and achieve
13 the same therapeutic effects. Despite this knowledge, Gilead did not reduce the TDF dose in Stribild.

14 370. Gilead knew, before its first TDF Drug and every subsequent TDF Drug was approved
15 by the FDA, that TAF is safer than TDF in that it reduces the risks of kidney and bone toxicities
16 associated with TDF. Despite knowing that TAF would reduce foreseeable harm to patients’ kidneys
17 and bones, Gilead repeatedly incorporated the TDF design into the TDF Drugs prior to FDA approval
18 and prevented patients from taking a safer TAF-based product so Gilead could make more money.

19 371. Based, *inter alia*, on its duty to monitor the adverse effects associated with Viread,
20 Truvada, Atripla, Complera, and Stribild, Gilead knew that the likelihood and severity of the harm
21 associated with TDF was great. Thousands of patients experienced damage to their kidneys and bones
22 as a result of TDF exposure—some of it severe and irreversible. The likelihood and severity of the
23 kidney and bone injuries suffered by patients like Plaintiffs far outweighed Gilead’s burden in taking
24 safety measures to reduce or avoid the harm. Gilead had already designed the safer TAF method of
25 introducing tenofovir into the body before it sought FDA approval for the TDF Drugs. Gilead had also
26 reduced the TAF dose when combined with cobicistat in Genvoya, when it was developing Stribild.

27 372. Gilead failed to exercise ordinary care in the design, manufacture, and sale of the TDF
28 Drugs.

1 373. Gilead failed to use the amount of care in designing the TDF Drugs that a reasonably
2 careful manufacturer would have used before FDA approval to avoid exposing patients to foreseeable
3 risks of harm.

4 374. Gilead undertook to develop and market a safer TAF-designed product to sell to
5 wholesalers and other direct purchasers of pharmaceuticals. Gilead recognized that its development
6 and marketing of safer TAF-designed products was for the protection of patients like Plaintiffs. By
7 shelving the safer TAF design purely for monetary gain and deceptively representing why it was
8 abandoning the safer TAF design, Gilead failed to exercise reasonable care in the performance of this
9 undertaking that increased the risk of harm to patients like Plaintiffs. Gilead's failure to exercise
10 reasonable care resulted in physical harm to Plaintiffs.

11 375. Gilead failed to use the amount of care in warning about the risks and safe use of the
12 TDF Drugs that a reasonably careful manufacturer would have used to avoid exposing patients to
13 foreseeable risks of harm.

14 376. Gilead knew or reasonably should have known that the TDF Drugs were dangerous or
15 likely to be dangerous when used in a reasonably foreseeable manner.

16 377. Gilead knew or reasonably should have known that Plaintiffs and Plaintiffs' physicians
17 would not realize the danger posed by inadequate monitoring of patients taking TDF Drugs.

18 378. Gilead failed to adequately warn Plaintiffs and Plaintiffs' physicians about the need to
19 monitor all patients taking the TDF Drugs. For years, Gilead failed to recommend that doctors monitor
20 anyone other than patients "at risk" for TDF-induced kidney and/or bone injuries. When Gilead finally
21 added a weak instruction regarding the monitoring of all patients for kidney damage, it only warned
22 doctors to monitor patients for one insufficient marker of kidney dysfunction that was incapable of
23 detecting many dangerous changes in kidney dysfunction, and failed to warn doctors to monitor TDF
24 patients on a frequent schedule. Gilead's monitoring warnings with respect to "at risk" Viread,
25 Truvada, Atripla, Complera, and Stribild users were also inadequate because they failed to warn
26 doctors to monitor patients on a specific, frequent schedule.

27 379. Gilead could have unilaterally strengthened its U.S. labels before FDA approval for all
28 TDF Drugs and after FDA approval for Viread, Truvada, Atripla, and Complera through July 2012.

1 380. A reasonable manufacturer and seller under the same or similar circumstances would
2 have instructed Plaintiffs and Plaintiffs' physicians on the safe use of the TDF Drugs, i.e., use where
3 doctors frequently monitored all TDF patients for TDF-associated toxicity, including monitoring for
4 kidney damage using more than one inadequate test. Gilead knew to warn doctors to frequently monitor
5 all patients for kidney damage using more than one inadequate test because it did so in the European
6 Union.

7 381. Gilead's failure to adequately warn Plaintiffs and Plaintiffs' doctors about the need to
8 monitor TDF Drug patients was compounded by Gilead's omissions to doctors during sales detailing
9 and other promotional activities. Gilead's misleading promotion of the TDF Drugs undermined the
10 efficacy of its existing (inadequate) warnings.

11 382. Plaintiffs were injured by using TDF in a reasonably foreseeable way.

12 383. The lack of adequate warnings was a substantial factor in causing Plaintiffs' injuries.

13 384. Had Gilead adequately warned Plaintiffs' doctors, Plaintiffs' doctors would have read
14 and heeded such adequate warnings.

15 385. Plaintiffs' properly warned physicians would have monitored Plaintiffs differently—by
16 frequently monitoring Plaintiffs using sufficiently sensitive markers of kidney function that would
17 have alerted doctors to early signs of nephrotoxicity, including tubular damage that leads to more
18 severe renal adverse events and bone mineral density loss. Once they recognized the signs of
19 nephrotoxicity, Plaintiffs' physicians would have taken further action after weighing their treatment
20 options, such as increased monitoring, less frequent dosing, or drug discontinuation, before the damage
21 manifested, worsened, or became irreversible. Plaintiffs' properly warned physicians would have
22 detected TDF toxicity earlier, thus preventing or lessening Plaintiffs' injuries.

23 386. Plaintiffs were injured as a direct and proximate result of Gilead's negligence.

24 387. Gilead's conduct constitutes gross negligence and willful misconduct.

25 388. By designing the TDF Drugs to contain TDF when it knew TDF harmed patients'
26 kidneys and bones, and intentionally withholding the safer TAF design from patients, while failing to
27 adequately warn of the known risks and safe use of TDF, Gilead acted in reckless disregard of, or with
28 a lack of substantial concern for, the rights of others. By designing Stribild to contain 300 mg TDF

1 when it knew to reduce the tenofovir prodrug dose with combined with cobicistat, Gilead acted in
2 reckless disregard of, or with a lack of substantial concern for, the rights of others.

3 389. Gilead intentionally designed the TDF Drugs to contain 300 mg TDF and withheld the
4 safer designs from patients while in disregard of the known risk of TDF-induced kidney and/or bone
5 toxicity, making it highly probable that harm would result.

6 390. Gilead knew that its conduct would harm patients like Plaintiffs but Gilead withheld its
7 safer designs to make more money.

8 **COUNT V**

9 **FRAUD BY OMISSION**
10 **UNDER THE LAWS OF THE STATES OF ALABAMA, GEORGIA, NEVADA, TEXAS,**
11 **AND VIRGINIA**

12 391. Plaintiffs reallege and incorporate the allegations made above as if fully set forth below.

13 392. Gilead has a duty to exercise ordinary care in the design, manufacture, marketing, and
14 sale of its pharmaceutical products, including the TDF Drugs.

15 393. Gilead has a duty to refrain from selling unreasonably dangerous products, including
16 the duty to ensure that its pharmaceutical products do not cause patients to suffer from foreseeable
17 risks of harm.

18 394. Gilead has a duty to monitor the adverse effects associated with pharmaceutical
19 products, including Stribild.

20 395. Gilead has a duty to exercise reasonable care when it undertakes affirmative acts for
21 the protection of others.

22 396. Gilead owes these duties to Plaintiffs because it was foreseeable to Gilead that patients
23 like Plaintiffs would ingest and consequently be endangered by the TDF Drugs.

24 397. Gilead also owed a duty to speak because it was in possession of information about
25 TDF and TAF that was not readily available to Plaintiffs and Plaintiffs' physicians, made partial
26 representations about TDF and TAF to Plaintiffs and Plaintiffs' physicians while suppressing material
27 facts, and actively concealed material information about TDF and TAF from Plaintiffs and Plaintiffs'
28 physicians, including that: (a) Gilead knew about the safer TAF design for delivering tenofovir into
the body prior to seeking and receiving FDA approval for the TDF Drugs but designed the TDF Drugs

1 to include TDF anyway, even though it knew that TDF posed a significant and increased safety risk to
2 patients' kidneys and bones; (b) the toxicity associated with tenofovir was not unavoidable; (c) the real
3 reason Gilead abandoned its TAF design in 2004 was not because TAF could not be sufficiently
4 differentiated from TDF; (d) Gilead had already determined that it should reduce the dose of tenofovir
5 prodrug when combining it with cobicistat at the time it was developing Stribild but Gilead did not
6 reduce the TDF dose in Stribild as it did with Genvoya; (e) Gilead purposefully withheld the TAF
7 design, which it knew was safer than TDF, solely to make more money; and (f) Gilead knew to warn
8 doctors to frequently monitor all patients for the adverse effects of TDF toxicity using more than one
9 insufficient marker of kidney function even though it did not do so in its warnings to doctors in the
10 U.S.

11 398. Gilead knew that this information was not readily available to Plaintiffs and their
12 doctors, and Plaintiffs and their doctors did not have an equal opportunity to discover the truth.
13 Plaintiffs and their doctors had no practicable way of discovering the true state and timing of Gilead's
14 knowledge.

15 399. Gilead intentionally omitted adequate warnings about the risks and safe use of TDF
16 when promoting the TDF Drugs to doctors and patients by, *inter alia*, omitting information about the
17 frequency and severity of adverse kidney and bone events and failing to tell doctors to adequately
18 monitor TDF patients for drug-induced toxicity.

19 400. Gilead intentionally omitted from its prescriber and patient labeling an adequate
20 warning regarding the need for doctors to monitor all TDF patients, on a frequent, specific schedule,
21 for the adverse effects of TDF-associated bone and kidney toxicity. Gilead intentionally omitted an
22 adequate monitoring warning in order to conceal the true risk of its TDF-based antiviral products, and
23 to inflate sales by inducing doctors to prescribe, and patients like Plaintiffs to consume, its TDF Drugs.
24 Gilead could have unilaterally strengthened its U.S. labels before FDA approval for all TDF Drugs
25 and after FDA approval for Viread, Truvada, Atripla, and Complera through July 2012.

26 401. By providing inadequate warnings that were contrary to those it gave with respect to
27 the exact same drugs in the EU, Gilead partially disclosed material facts. Gilead had a duty of complete
28 disclosure once it began to speak.

1 402. Plaintiffs and their doctors justifiably relied on Gilead's product labeling and other
2 representations.

3 403. Had Gilead not omitted this information about the safe use of its drugs from the
4 prescriber and patient labeling, doctors would have performed, and patients would have insisted upon,
5 frequent and adequate monitoring for the kidney and bone problems that have injured Plaintiffs. But
6 for Gilead's omissions, Plaintiffs would have consumed the TDF Drugs in a safer way.

7 404. If Plaintiffs had been adequately monitored for kidney and bone problems while taking
8 TDF, they would not have been injured or their injuries would have been less severe.

9 405. Gilead intentionally concealed from Plaintiffs and their doctors the fact that Gilead had
10 already developed the safer TAF mechanism but designed the TDF Drugs to contain TDF instead of
11 the safer TAF design in order to maximize profits on its TDF-based products and extend its ability to
12 profit on its HIV franchise for years to come.

13 406. Gilead also intentionally concealed from Plaintiffs and their doctors that Gilead knew
14 that the tenofovir prodrug dose should be reduced when combined in a fixed dose combination pill
15 with cobicistat, but did not reduce the TDF dose in Stribild as it did with Genvoya.

16 407. By concealing that Gilead was aware of but had withheld the safer designs, Gilead
17 intended to and did induce Plaintiffs' doctors to prescribe, and Plaintiffs to ingest, one or more of the
18 TDF Drugs, thereby causing Plaintiffs' injuries.

19 408. Plaintiffs and their doctors justifiably relied on Gilead's omissions regarding TAF.

20 409. Had Gilead disclosed that it was aware of, but intentionally withheld, the safer TAF
21 mechanism for delivering tenofovir into the body, Plaintiffs would have ingested TDF in a safer
22 manner.

23 410. Plaintiffs' doctors would have ensured that Plaintiffs ingested TDF in a safer manner
24 through increased and/or more careful monitoring for TDF-induced kidney and bone toxicity, or by
25 prescribing TDF without coadministration with cobicistat.

26 411. Plaintiffs were injured as a direct and proximate result of Gilead's material omissions.
27
28

COUNT VI

BREACH OF IMPLIED WARRANTY OF MERCHANTABILITY UNDER THE LAWS OF THE STATES OF ALABAMA, NEVADA, TEXAS, AND VIRGINIA

412. Plaintiffs reallege and incorporate the allegations made above as if fully set forth below.

413. Gilead is the manufacturer and seller of the TDF Drugs.

414. An implied warranty of fitness for human consumption runs from Gilead to consumers like Plaintiffs.

415. Gilead impliedly warranted to Plaintiffs and their doctors that the TDF Drugs were of merchantable quality, and fit and safe for the use for which they were intended.

416. Plaintiffs ingested the TDF Drugs for the treatment of HIV, Hepatitis B, or PrEP, which is the purpose for which the drugs were manufactured, sold, and prescribed.

417. Plaintiffs relied on Gilead's skill or judgment to provide a product suitable for this purpose. Gilead is in the business of designing, manufacturing, selling, and marketing prescription drugs and specializes in drugs for the treatment or prevention of HIV, and treatment of Hepatitis B.

418. Gilead had reason to know that Plaintiffs and their doctors would rely on Gilead's skill or judgment.

419. The TDF Drugs are unfit for the purpose for which they were purchased because they are toxic to patients' kidneys and bones when put to their intended and ordinary use, causing injuries to Plaintiffs.

420. The dangers the TDF Drugs posed to Plaintiffs' kidneys and bones were known and knowable to Gilead at the time of manufacture and sale. Yet Gilead marketed the TDF Drugs without adequate warnings about the risks or safe use of TDF of which it knew or should have known.

421. Plaintiffs suffered kidney and/or bone injuries as a result of ingesting the TDF Drugs.

422. In addition to the common law, the conduct alleged herein constitutes a breach of the implied warranty of merchantability under the Uniform Commercial Code as codified the following statutes:

a. Alabama, Code of Alabama § 7-2-314;

b. Nevada, Nev. Rev. Stat. § 104.2314;

1 c. Texas, Tex. Bus. & Com. Code § 2314; and

2 d. Virginia, Va. Code Ann. § 8.2-314.

3 423. On October 8, 2020, Plaintiffs sent a letter to Gilead via certified mail giving official
4 notice of Gilead's breach of the implied warranty of merchantability under the laws of Alabama,
5 Nevada, Texas, and Virginia. The notice letter is attached as Exhibit A.

6 **COUNT VII**

7 **VIOLATION OF STATE CONSUMER PROTECTION LAWS**

8 424. Plaintiffs reallege and incorporate the allegations made above as if fully set forth below.

9 425. Plaintiffs are consumers within the meaning of the following states' consumer
10 protection laws because they are natural persons who purchased one or more of the TDF Drugs for
11 personal, family, or household use.

12 426. The TDF Drugs are goods and merchandise within the meaning of the following states'
13 consumer protection laws.

14 427. Gilead manufactured, sold, and marketed its TDF Drugs in trade or commerce,
15 including within each of the 50 U.S. States.

16 428. Gilead engaged in unconscionable, unfair, false, fraudulent, misleading, and deceptive
17 acts and practices in connection trade or commerce involving its TDF Drugs.

18 429. Gilead engaged in unfair and/or unconscionable conduct by knowingly designing its
19 TDF Drugs to be unreasonably dangerous before FDA approval and withholding the safer designs to
20 make more money.

21 430. Gilead also intentionally suppressed, concealed, and omitted material facts about the
22 risks and benefits of the TDF Drugs in its promotional, marketing, and/or labeling communications to
23 Plaintiffs and Plaintiffs' doctors, including, but not limited to: (1) the true frequency and severity of
24 the risks of TDF to kidneys and bones; (2) that all TDF patients should be carefully monitored for
25 adverse kidney and bone effects on a frequent schedule in light of the true risks of TDF; (3) that Gilead
26 had already developed the safer TAF design for delivering tenofovir into the body but nevertheless
27 designed the TDF Drugs to contain TDF, and withheld the safer TAF design, in order to avoid
28 admitting the toxicity of TDF, maximize profits on its TDF-based products, and extend its ability to

1 profit on its HIV franchise for years to come; and (4) Gilead knew that the tenofovir prodrug dose
2 should be reduced when combined in a fixed dose combination pill with cobicistat, but did not reduce
3 the TDF dose in Stribild.

4 431. Gilead had a duty to disclose the omitted material facts about TDF and TAF because it:
5 (a) was in possession of information about TDF and TAF that was not readily available to Plaintiffs
6 and Plaintiffs' physicians; (b) made partial representations about TDF and TAF to Plaintiffs and
7 Plaintiffs' physicians while suppressing material facts; and (c) actively concealed material information
8 about TDF and TAF from Plaintiffs and Plaintiffs' physicians.

9 432. Gilead's conduct significantly impacted the public as actual or potential consumers of
10 Gilead's TDF Drugs. Hundreds of thousands of consumers in the U.S. have ingested one or more of
11 the TDF Drugs and Gilead has directed its misleading marketing and promotional messages to the
12 market generally. Consumers like Plaintiffs are at an informational disadvantage and lack bargaining
13 power relative to Gilead. Gilead's conduct has previously impacted other consumers and has
14 significant potential to do so in the future.

15 433. Gilead's conduct was likely to mislead and did mislead reasonable consumers and
16 members of the public.

17 434. Gilead's omissions were material and affected Plaintiffs' and Plaintiffs' doctors'
18 conduct.

19 435. Gilead intended that others rely on its deceptive and misleading omissions regarding its
20 TDF Drugs.

21 436. Plaintiffs and their doctors reasonably relied on Gilead's deceptive and misleading
22 omissions regarding its TDF Drugs.

23 437. Plaintiffs' doctors prescribed, and Plaintiffs ingested, one or more of the TDF Drugs in
24 reliance on Gilead's unconscionable, false, misleading and/or deceptive acts and omissions.

25 438. Plaintiffs were directly and proximately injured as a result of Gilead's deceptive
26 conduct. But for Gilead's unfair and/or unconscionable conduct, Plaintiffs would have ingested a safer
27 tenofovir-prodrug product, thus preventing or reducing Plaintiffs' injuries and monetary expenses in
28 connection with taking TDF. But for Gilead's omissions, Plaintiffs would have ingested the TDF Drugs

1 in a safer way—through more careful, frequent monitoring and/or by not taking Stribild (TDF in
2 combination with cobicistat)—thus preventing or reducing Plaintiffs’ injuries and monetary expenses
3 in connection therewith.

4 439. Plaintiffs suffered ascertainable losses as a result of Gilead’s violations of the state
5 consumer protection statutes alleged herein. Plaintiffs will prove the full extent and amount of their
6 damages at trial.

7 440. The conduct alleged herein violates the state consumer protection statutes as further
8 alleged below.

9 **a. Alabama: Ala. Code §§ 8-19-1 *et seq.***

10 441. Alabama Plaintiffs intend to assert a claim under the Alabama Deceptive Trade
11 Practices Act, alleging that Gilead committed unconscionable, false, misleading and/or deceptive acts
12 and practices in the conduct of trade or commerce in violation of Ala. Code § 8-19-5(27), and violated
13 Ala. Code § 8-19-5(5) and (7) by deceptively representing, through partial representations and
14 omissions, that the TDF Drugs have characteristics, benefits, and qualities they do not have, and are
15 of a particular standard and quality when they are another.

16 442. On October 8, 2020, Alabama Plaintiffs made a written demand for relief in satisfaction
17 of the Act and will amend this Complaint to add claims under the Act once the required notice period
18 has elapsed. The notice letter is attached as Exhibit A.

19 443. These paragraphs are included for notice purposes only and are not intended to assert a
20 claim under the Alabama Deceptive Trade Practices Act at this time.

21 **b. Nevada: Nev. Rev. Stat. §§ 598.0903 *et seq.***

22 444. Gilead committed a deceptive trade practice within the meaning of Nev. Rev. Stat.
23 §§ 598.0903 *et seq.* by: 1) deceptively representing, through partial representations and omissions, the
24 characteristics and benefits of the TDF Drugs in violation of Nev. Rev. Stat. §§ 598.0915(5);
25 2) deceptively representing, through partial representations and omissions, that the TDF Drugs are of
26 a particular standard or quality when it knew they are of another standard or quality in violation of
27 Nev. Rev. Stat. §§ 598.0915(7); and 3) knowingly failing to disclose a material fact in connection with
28 the sale of the TDF Drugs in violation of Nev. Rev. Stat. §§ 598.0923(2).

1 445. Nevada Plaintiffs were damaged as a result of Gilead's violations of Nev. Rev. Stat.
2 §§ 598.0903 *et seq.*

3 446. Nevada Plaintiffs seek actual damages, costs of suit, and reasonable attorneys' fees.

4 **c. Texas: Tex. Bus. & Com. Code Ann. §§ 17.41 *et seq.***

5 447. Gilead's conduct constitutes false, misleading, or deceptive acts or practices in the
6 conduct of trade or commerce in violation of Tex. Bus. & Com. Code Ann. § 17.46(a).

7 448. Gilead deceptively represented, through partial representations and omissions, the TDF
8 Drugs as having characteristics or benefits that they do not in violation of Tex. Bus. & Com. Code
9 Ann. § 17.46(b)(5).

10 449. Gilead deceptively represented, though partial representations and omissions, that the
11 TDF Drugs are of a particular standard or quality that they are not in violation of Tex. Bus. & Com.
12 Code Ann. § 17.46(b)(7).

13 450. Gilead deceptively represented, through partial representations and omissions, that a
14 warranty conferred or involved rights which it does have or involve in violation of Tex. Bus. & Com.
15 Code Ann. § 17.46(20).

16 451. Gilead failed to disclose information concerning the TDF Drugs which was known at
17 the time of the transaction if such failure to disclose such information was intended to induce the
18 consumer into a transaction into which the consumer would not have entered had the information been
19 disclosed in violation of Tex. Bus. & Com. Code Ann. § 17.46(b)(24).

20 452. Gilead knowingly and intentionally violated the Texas Deceptive Trade Practices-
21 Consumer Protection Act.

22 453. Texas Plaintiffs suffered economic damages as a result of Gilead's violations of Tex.
23 Bus. & Com. Code Ann. § 17.46.

24 454. Texas Plaintiffs intend to seek economic damages, three times Plaintiffs' economic
25 damages and mental anguish damages in light of Gilead's knowing and intentional violations, and
26 reasonable and necessary attorneys' fees and court costs.

27 455. On October 8, 2020, Texas Plaintiffs made a written demand for relief in satisfaction
28 of the Texas Deceptive Trade Practices-Consumer Protection Act and will amend this Complaint to

1 add claims for damages under the Act once the required notice period has elapsed. The notice letter is
2 attached as Exhibit A.

3 456. These paragraphs are included for notice purposes only and are not intended to assert a
4 claim for damages under the Texas Deceptive Trade Practices-Consumer Protection Act at this time.

5 **PRAYER FOR RELIEF**

6 Wherefore, Plaintiffs request that the Court enter an order or judgment against Gilead and in
7 favor of Plaintiff, and grant the following relief:

8 A. Declare, adjudge, and decree the conduct of Gilead as alleged herein to be unlawful,
9 unfair, and/or deceptive and otherwise in violation of the law;

10 B. Award Plaintiffs actual, compensatory, and/or statutory damages in an amount to be
11 proven at trial;

12 C. Award Plaintiffs punitive and exemplary damages as permitted by law and the statutes
13 cited herein in an amount to be proven at trial;

14 D. Award Plaintiffs restitution and restitutionary disgorgement to restore ill-gotten gains
15 received by Gilead as a result of the unfair, wrongful, and deceptive conduct alleged herein;

16 E. Award Plaintiffs the costs of bringing this suit, including reasonable attorneys' fees;
17 and

18 F. Award Plaintiffs such other and further relief as to which Plaintiffs may be entitled in
19 law or equity.

20 **JURY DEMAND**

21 Pursuant to Federal Rule of Civil Procedure 38(c), Plaintiffs demand a trial by jury on all
22 matters so triable.

1 DATED: October 9, 2020

Respectfully submitted,

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