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Paper 16
Date: February 5, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GILEAD SCIENCES, INC.,
Petitioner,

v.

THE UNITED STATES OF AMERICA,
REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH & HUMAN SERVICES,
Patent Owner.

IPR2019-01455
Patent 9,937,191 B2

Before ZHENYU YANG, CHRISTOPHER M. KAISER, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Gilead Sciences, Inc. ("Petitioner"),[1] on August 23, 2019, filed a Petition to institute *inter partes* review of claims 1–19 of U.S. Patent No. 9,937,191 B2 (Ex. 1005, "the '191 patent"). Paper 1 ("Pet." or "Petition"). The United States of America ("Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp."). We granted (Paper 13) Petitioner's request to file a pre-institution Reply to Patent Owner's Preliminary Response to address certain issues pertaining to whether the Petition should be denied on a discretionary basis under 35 U.S.C. § 325(d). Paper 14. We also permitted Patent Owner to file a Sur-Reply to Petitioner's authorized Reply. Paper 15.

Under 35 U.S.C. § 314(a), *inter partes* review may not be instituted unless the Petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." We conclude that Petitioner has not established a reasonable likelihood of prevailing on its assertion that claims 1–19 are unpatentable based on the grounds advanced. Thus, for reasons further explained below, we do not institute *inter partes* review of claims 1–19 of the '191 patent.

A. *Related Patents & Proceedings*

The '191 patent issued April 10, 2018, from U.S. Patent Application No. 15/406,344 ("the '344 Application"), which was filed January 13, 2017. The '344 Application is a continuation of U.S. Patent Application No.

[1] Petitioner identifies itself as the real party-in-interest. Pet. 1.

14/679,887 ("the '887 Application"), filed on April 6, 2015, which itself is a continuation of U.S. Patent Application No. 11/669,547 ("the '547 Application"), filed January 31, 2007. Ex. 1005, 1:7–13.[2]

The '887 Application and the '547 Application issued, respectively, as U.S. Patent No. 9,579,333 B2 (issued February 28, 2017) and U.S. Patent No. 9,044,509 B2 (issued June 2, 2015). *See* Exs. 1003 ("the '333 patent") and 1001 ("the '509 patent"). In addition to the above patents/applications, U.S. Patent Application No. 15/913,750 ("the '750 Application") is a continuation of the '344 Application, and the '750 Application issued as U.S. Patent No. 10,335,423 B2, on July 2, 2019. Ex. 1007 ("the '423 patent").

Beyond the instant Petition, Petitioner concurrently filed three petitions for *inter partes* review of the above-noted, related patents. Pet. 1. Those proceedings are: IPR2019-01453 (challenging claims in the '509 patent); IPR2019-01454 (challenging claims in the '333 patent); and IPR2019-01456 (challenging claims in the '423 patent). *Id.*

Patent Owner identifies a related lawsuit. Paper 10, 1. That is, on November 6, 2019, Patent Owner filed a complaint alleging infringement by Petitioner of the four patents identified above. *Id.*; *see generally* Ex. 2018 (Complaint in *United States v. Gilead Sciences, Inc. & Gilead Sciences Ireland UC*, Case No. 1:19-cv-02103-MN (D. Del. Nov. 6, 2019)).

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[2] These applications further claim the benefit of U.S. Provisional Patent Application No. 60/764,811, filed February 3, 2006. Ex. 1005, 1:7–13.

B. *Asserted Grounds of Unpatentability*

Petitioner asserts two grounds of unpatentability in this Petition (Pet. 5), which are provided in the table below:

Claims Challenged	35 U.S.C. §	Reference(s)
1–19	102(b)[3]	Szekeres[4]
1–19	103(a)	Smith,[5] Szekeres

[3] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the '191 Patent have an effective filing date before the effective date of the applicable AIA amendments, we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103 in this Decision.

[4] Greg Szekeres et al., *Anticipating the Efficacy of HIV Pre-Exposure Prophylaxis (PrEP) and the Needs of At-Risk Californians*, (Nov. 2004) (Ex. 1011, "Szekeres"). The Petition uses the name "Cal-PrEP" for this reference. *See, e.g.*, Pet. 28–29. We, however, use the name Szekeres when referring to the reference, which nomenclature (using the lead author's last name) is more consistent with Office practice and the prosecution history. *See, e.g.*, Ex. 1006, 59–60 (Examiner using the name "Szekeres" for this reference). Petitioner provides evidence that Szekeres was publicly available by at least November or December, 2004. Pet. 28 (citing exhibits). Based on Petitioner's evidence (uncontested at present), we find that Szekeres is prior art for purposes of this Decision. Unless otherwise indicated, we use the pagination appearing on the exhibit copies entered in this record. *See, e.g.*, Ex. 1011, cover-1, 7, 11, etc.

[5] Dawn K. Smith et al., *Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States*, 54:RR-2 MORBIDITY AND MORTALITY WEEKLY REPORT, (Jan. 21, 2005) (Ex. 1012, "Smith"). The Petition describes this reference as "CDC-PEP" (*see, e.g.*, Pet. 29–30), but we use the name "Smith" for the same reasons as noted above (*supra* n.4). Ex. 1006, 59–60 (using the name "Smith" during prosecution). We also accept for purposes of this Decision

Petitioner also relies on the declaration of Michael Youle, MB ChB, among other evidence. Ex. 1009 ("Youle Decl.").

C. *The '191 Patent*

The '191 patent is titled "INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS." Ex. 1005, (54). According to the patent, a "process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus," and "[p]rotection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor [(NRTI)] and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor [(NtRTI)] prior to exposure to the immunodeficiency retrovirus." *Id.* at Abstr.; *see also id.* at 1:22–28 ("The present invention in general relates to a process for inhibiting initial infection by a retrovirus such as human immunodeficiency virus (HIV) . . . even in response to multiple viral challenges.").

The '191 patent explains that, despite progress in slowing the advancement of symptoms of AIDS associated with HIV infection, without an effective vaccine, HIV infection continues to spread globally. *Id.* at 1:30–32. The '191 patent further explains that current treatments involving monitoring viral titers and starting highly active antiretroviral therapy (or "HAART") when the titer exceeds a threshold "has not prevented new infections." *Id.* at 1:37–41.

Petitioner's contentions and evidence (uncontested here) that Smith was publicly available before February 3, 2005. Pet. 29–31.

According to the '191 patent, "[a]n attractive method of controlling the spread of HIV would be to provide an individual exposed to a potential source of HIV with a pre-exposure prophylactic treatment." *Id.* at 1:42–44. However, the patent explains, "[p]revious attempts at pre-exposure prophylaxis have met with limited success." *Id.* at 1:52–53, 1:67–2:2 ("It is also unknown if initiating HAART therapy in a pre-exposure prophylactic regimen would be efficacious."). Thus, "society remains devoid of a pre-exposure prophylactic regimen to prevent an individual from developing self-propagating retrovirus infection subsequent to initial exposure," and "there exists a need for a chemoprophylactic composition and dosing regimen effective in blocking early stage infection by retrovirus in a host founder cell population." *Id.* at 2:2–8.

The '191 patent discloses that "[t]he combination of NRTI and NtRTI compounds administered prophylactically according to the present invention are shown to provide a dose-dependent inhibition of HIV self-replicating infection and a therapeutically effective dosing primate host protection against self-replicating HIV infection is provided, even in response to multiple viral challenges." Ex. 1005, 3:66–4:5. As preferred compounds for use in the invention's prophylactic combination therapy, the patent identifies emtricitabine (as the NRTI) and tenofovir (as the NtRTI), as well as prodrugs of tenofovir. *See id.* at 7:45–59 (Example 1, describing oral administration of emtricitabine (also known as "FTC") and tenofovir disoproxil fumarate ("TDF"), a prodrug of tenofovir); *see also id.* at 4:60–67 ("An exemplary NtRTI prodrug currently FDA approved for HAART use is

tenofovir disoproxil fumarate (TDF).").[6]

The '191 patent describes, in examples, testing that compares the protection against a retroviral challenge provided by the disclosed combination therapy versus monotherapies, and no therapeutic treatment. *See, e.g.*, Ex. 1005, 9:5–10:13 (Examples 7 and 8), Figs. 1–2. More specifically, the '191 patent describes a comparison of groups of primates (i.e., macaques) receiving a combination of agents (Groups 2 and 3), macaques receiving therapy with a single agent (Group 1, FTC only (subcutaneous), n=6), and a control arm of subjects (n=18) receiving no treatment. *Id.* at 9:5–24. The Group 2 macaques (n=6) received oral administration of FTC and TDF, and the Group 3 macaques (n=6) received subcutaneous administration of FTC and tenofovir. *Id.* at 9:17–22, Fig. 1. The macaques in the experimental and control groups are exposed to weekly viral challenges (for up to 14 weeks), and the viral challenges for any particular macaque were terminated once that subject became infected. *Id.* at 9:7–15, Fig. 1.[7]

Results of this testing are described in the '191 patent and illustrated in, for example, Figure 2, which is reproduced below.

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[6] According to the patent, the FTC and TDF amounts given in Example 1 are comparable to a 200 mg FTC and 300 mg TDF oral dosing in humans. Ex. 1005, 7:45–59; *see also id.* at 6:59–61 (describing an "inventive kit" with oral tablet doses, and that, "[f]or an adult human, preferably each of the doses includes 200 mg of emtricitabine and 300 mg TDF").

[7] Further details about, *inter alia*, the dosing amounts and routine, the manner of the viral challenge, and the measurement and statistical methods used are described in the examples. *See, e.g.*, Ex. 1005, 7:45–8:10 (Examples 1–2, describing inoculations with the SHIV viral isolate).

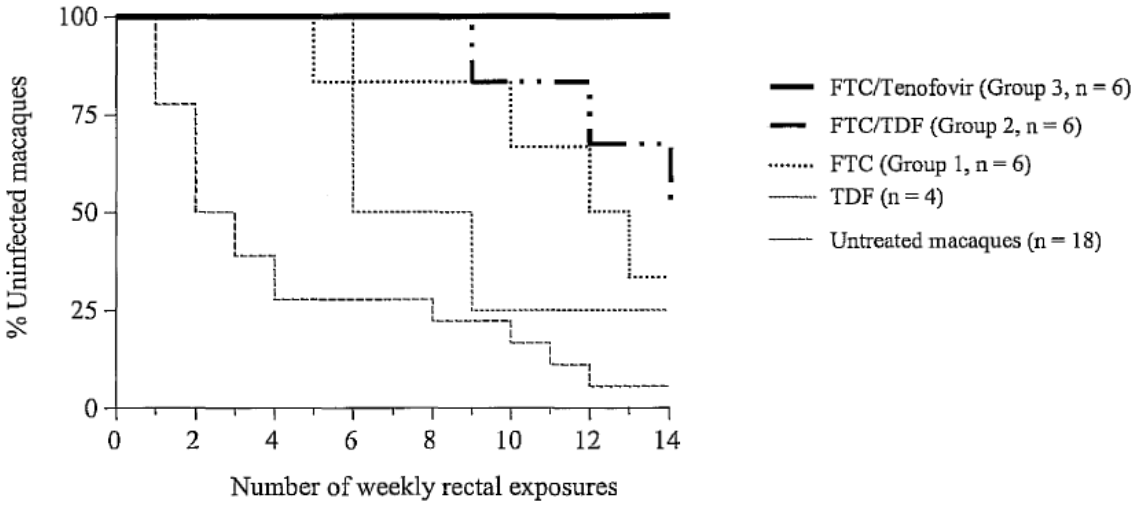

FIG. 2

Ex. 1005, Fig. 2. Figure 2 shows survival curves for the groups of primates tested according to Example 7 of the '191 patent, plotted as a percent of uninfected subjects relative to the number of weekly viral exposures. *Id.* at 9:36–10:12. Data for monotherapy with TDF (n=4) is also shown. *Id.* at 9:39–40. As the patent explains, "[u]ntreated macaques are infected after a median of two rectal exposures . . . [and] the majority of the [control] animals (13/18 or 72%) are infected during the first 4 challenges." *Id.* at 9:40–45. "[O]nly one (6%)" of the control subjects "remained uninfected after 14 exposures." *Id.* In contrast, "[a]ll 6 macaques in Group 3 [FTC plus tenofovir] . . . remained uninfected demonstrating that full protection against repeated challenges is possible." *Id.* at 9:51–54. And, "[o]f the 6 macaques in Group 2 [FTC plus TDF], 4 were protected and only 2 . . . became infected at exposures 9 and 12," demonstrating that "[c]ompared to controls, infection in this group is reduced by 7.8 fold." *Id.* at 9:54–60 ("[i]nfection in both [Group 2] animals is significantly delayed compared to untreated

controls," with infection at weeks 10 and 12).[8]

D. *Challenged Claims*

The '191 patent includes two independent claims, and several dependent claims. The independent claims, claims 1 and 13, are illustrative and read as follows:

> 1. A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:
>
> (a) selecting a primate host not infected with the immunodeficiency retrovirus, and
>
> (b) administering directly to an uninfected primate host a combination comprising:
>
> i. a pharmaceutically effective amount of emtricitabine; and
>
> ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate,
>
> wherein the combination is administered orally in tablet form prior to the exposure of the primate host to the immunodeficiency retrovirus,
>
> thereby protecting the primate host from infection with the immunodeficiency retrovirus.
>
> 13. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:
>
> (a) selecting an uninfected human that does not have the self-replicating infection; and

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[8] For Group 1 (FTC only), 2 of the 6 macaques remained uninfected at week 14, which the patent indicates is a 3.8-fold reduction in infection compared to the control. Ex. 1005, 9:63–10:4. Figure 2 indicates that 1 of the 4 macaques receiving TDF monotherapy remained uninfected at week 14. *See id.* at 10:8–12, 11:51–58 (citing a study by "Subbarao" (Ex. 1050)).

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine in a tablet; and

ii. a pharmaceutically effective amount of tenofovir or a tenofovir disoproxil fumerate in a tablet;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus.

Ex. 1005, 12:32–47, 13:13–14:2.

E. *Prosecution History*

We provide an overview of the file history for the '191 patent, as well as summaries of relevant portions of the prosecution of the '191 patent's parent and grand-parent applications, which applications issued respectively as the '333 patent and the '509 patent. Ex. 1002 (file history for the '509 patent); Ex. 1004 (file history for the '333 patent); Ex. 1006 (file history for the '191 patent). The same Examiner handled prosecution for all the related patents relevant to this Petition—the '509, '333, '191, and '423 patents.

The '191 patent / '344 Application

The application that issued as the '191 patent was filed January 13, 2017. Ex. 1005; Ex. 1006, 110–160; *see id.* at 130–132 (claims 1–19 as filed). On August 8, 2017, the Examiner entered a rejection of claims 1–19

for obviousness. Ex. 1006, 55–62.[9] That rejection was based on a combination of references: "Stephenson," "Dahl," "Shapiro," "Smith," "Szekeres," "Keller," and "AIDS PATIENT CARE and STDs." *Id.* at 59–61. Szekeres and Smith in this rejection are the same references asserted in the Petition.

At the time of that rejection, the Examiner made a number of findings about the cited art. Among other things, the Examiner determined that Dahl taught combinations of emtricitabine (i.e., FTC) and tenofovir prodrugs (e.g., TDF) as having anti-HIV activity. *Id.* at 59. Further, the Examiner noted, Dahl taught that tenofovir "has been known for both the treatment and prophylaxis of HIV infection," and that formulations of Dahl's compositions (e.g., topical applications) "may be administered for either therapeutic or prophylactic use." *Id.*

Because the Examiner found Dahl did not teach "expressly [the] treatment of a subject who has not [been] infected with the immunodeficiency virus with the particular combination of emtricitabine and tenofovir," the Examiner cited several other references, including Szekeres and Smith. *Id.* at 60. With respect to Szekeres, the Examiner stated that it "teach[es] that it is widely believed in the art that biomedical approaches to HIV prevention" are "required to adequately curb the spread

[9] The Examiner also rejected the claims for obviousness-type double patenting over claims in the related '509 and '333 patents (Ex. 1006, 57–58), which rejections were overcome after applicant filed a terminal disclaimer. *Id.* at 33 (noting that the terminal disclaimer has been reviewed and accepted).

of the virus, both by post exposure prophylaxis (PEP) and pre exposure prophylaxis (PreP)." *Id.* ("Known anti-HIV agents are used as the biomedical agents, tenofovir disoproxil fumarate (TDF), and a prodrug of tenofovir"). For Smith, the Examiner stated that it "reveal[s] US DHHS recommend[s] PEP treatment of those exposed to HIV with the known anti-HIV drugs, including emtricitabine, tenofovir, and their combination, Truvada), (200mg . . . emtricitabine/300mg tenofovir)." *Id.* 59–60 (also making findings as to the teachings of Keller, Shapiro, and other references).

From the cited references, the Examiner determined it would have been obvious to treat an uninfected subject at risk for exposure to HIV with a composition comprising the combination therapy (i.e., "Truvada®"). *Id.* at 60–61. The Examiner reasoned that the ordinarily skilled person would have been motivated to practice the claimed subject matter with a reasonable expectation of success "because it is known that anti-HIV agents will reduce the risk of HIV infection . . . [and] Truvada[] is known for treatment/prophylaxis of HIV infection." *Id.* at 61 ("employment of anti-HIV agents for prophylactic purpose against HIV infection is old and well-known, the employment of particular known anti-HIV agents would have been obvious"). Further, the Examiner reasoned, determining "effective amounts" and the "schedule" and "timing" for administering the anti-HIV regimen was routine activity "within the purview of ordinary skill." *Id.*

Following that rejection, the applicant participated in an interview with the Examiner, which is summarized in the record. Ex. 1006, 53 (Summary of October 3, 2017, interview). The interview summary indicates that the parent application and '509 patent were discussed, that the pending

claims would be "amended to [be] the same as claim 1 in '509, but with a further limitation of the oral dosage form: a tablet," and that "examiner indicates that such a claim would be allowable for reasons as set forth in the parent application." *Id.*; *see also id.* at 40 (remarks from applicant indicating that the claims would be amended as discussed, that the Examiner confirmed it would not be necessary to respond further to the pending rejection, and similarly that the Examiner confirmed it would not be necessary to resubmit any evidence provided during the '509 patent's prosecution).

Shortly thereafter, the Examiner entered a notice of allowability for claims 1–19. Ex. 1006, 31–34. According to the Examiner, "[t]he claims are allowable for reasons as set forth in parent application 11/669,547 [the '509 patent]." *Id.* at 33 (citing "interview summary of October 4, 2017").

To better understand the Examiner's bases for allowing the '191 patent's claims, we consider the file histories for the parent applications.

The '509 patent / '547 Application

The prosecution record of the '509 patent is lengthy, involving, among other things, multiple RCEs (Requests for Continued Examination) and an appeal to the Board that did not reach a decision (due to reopening of the prosecution before the Examiner). We do not summarize all the '509 patent's prosecution here.

Several years after the '547 Application was filed, the applicant provided a new set of claim amendments, along with argument and evidence in support of the patentability of the newly added/amended claims. Ex. 1002 (Amendment and Remarks dated July 21, 2014), 111–120. One of the newly added claims was claim 22, which (with a minor amendment) later became

claim 1 of the '509 patent.[10] *Id.* at 107. The pending rejection at that time, which was addressed in appellant's remarks, was for obviousness over "Stephenson," "Keller," "Shapiro," and "Collier." *Id.* at 111–120.

In the July 2014 Remarks, applicant raised a number of arguments. For example, applicant argued that the cited references did not teach "[p]rotection against a future infection," which "is distinct and different from treatment of an existing infection." *Id.* at 113–114. Moreover, applicant argued, there was no "reasonable expectation of success" in arriving at the claimed subject matter because "the art teaches that use of an anti-HIV agent to treat HIV infection does not reasonably predict the ability of that agent to protect against HIV infection." *Id.* at 115–118 (citing evidence, including Subbarao (Ex. 1050, here), "that many others have tried and failed to successfully avoid the establishment of an HIV infection, even with tenofovir itself"); *see also id.* at 117 ("Although infection was delayed in treated macaques, compared with control macaques, all animals still became infected by 11 weeks. *See* Subbarao et al. at page 907, figure 1."); Ex. 1050, 905 (Fig. 1).

In addition, the applicant argued and presented evidence of objective indicia of nonobviousness—in particular, evidence of unexpected results with the claimed combination therapy. Ex. 1002, 118–119. Citing, for instance, Example 7 of the Specification and a publication from the scientific literature ("Garcia-Lerma," or Ex. 1155, here) detailing a similar

[10] Claim 1 of the '509 patent is similar to claim 1 of the '191 patent. *Compare* Ex. 1001, 12:37–53 (claim 1 of '509 patent) *with* Ex. 1005, 12:32–47 (claim 1 of the '191 patent).

study on macaques receiving a series of viral challenges, the applicant argued that the data "showed that an exemplary claimed combination comprising FTC and TDF reduced the risk of rectal infection by 7.8-fold in an SIV macaque model." Ex. 1002, 119; Ex. 1155, 1. Citing another publication by Garcia-Lerma, applicant argued that data "showed that the study group which received FTC and TDF on various dosing schedules showed reduced risk of infection by **16.7**-fold relative to untreated controls," a "superior result" that "could not have been predicted from the cited prior art." Ex. 1002, 119. And, citing a clinical trial and publication by Grant (Ex. 2004 or "Grant-2010" here), applicant asserted that this data showed that "test subjects who had detectable blood levels of a study test drug combination (FTC and TDF) decreased their odds of an HIV infection by 92-95%." *Id.* at 119–120; Ex. 2004, 2596–2597 ("odds of HIV infection were lower by a factor of 12.9 . . . corresponding to a relative reduction in HIV risk of 92%. . . . After adjustment for reported unprotected receptive anal intercourse, the relative risk reduction was 95%"). Accordingly, applicant argued, "the references cited . . . as well as the specification of the present application" evidence "that the claims provide an unexpected superior result." Ex. 1002, 119–120.

About five months later, applicant and the Examiner participated in an interview. Ex. 1002, 99 (Summary of December 16, 2014, interview). At the interview, the pending claims, "particularly, claim 22 (new)" were discussed. *Id.* Moreover, as the interview summary indicates, applicants discussed "the unpredictability of HIV art, particularly in the aspect of prevention, or prophylactic treatment," and the Examiner noted the "several

post filing publications . . . supporting the alleged unexpected benefit residing in [the] claimed invention" that were submitted with the applicant's July 2014 remarks. *Id.* The Examiner "indicate[d] that all evidences will be fully and carefully reviewed." *Id.*

In a summary of a follow-up interview that occurred several days later, the Examiner indicated that "Dahl"[11] and the other cited references, as well as the "Grant" publication, were discussed. Ex. 1002, 78 (Summary of December 19, 2014, interview). The Examiner explained that Dahl teaches "the combination of tenofovir and emtricitabine for treating HIV" as well as suggesting applications for prophylaxis. *Id.* The Examiner noted, however, that "applicants' amendments, remarks submitted July 21, 2014 and all exhibit[s], evidences presented . . . have been fully considered and found persuasive as to claims 22 and 33 with a limitation that the administration is oral administration." *Id.* As the Examiner explained, "such claims are allowable in view of the high unpredictability of chemoprophylaxis against HIV infection and the supe[r]ior and unexpected results shown in the application and exhibits. Particularly, [the] Grant reference." *Id.*

The Examiner then later added to these comments in the "statement of reasons for allowance." Ex. 1002, 81. There, the Examiner explained, *inter alia*, that "the application shows that the [claimed] combination has superior effect as compared to tenofovir alone in animal model and evidences on the record has shown the claimed combination has clinically significant results,

[11] Dahl, as referred to by the Examiner, is WO 2004/064845 A1 (Ex. 1152).

which would have not been expected in view of the prior art as a whole." *Id.* at 81–82 (citing Grant-2010).

The '333 patent / '887 Application

A few months after indicating that the claims of the '509 patent were allowable, the Examiner rejected similar pending claims in the child '887 Application as obvious over the combination of Stephenson, Dahl, Shapiro, Keller, and AIDS PATIENT CARE and STDs. *See, e.g.*, Ex. 1004, 77–84 (Office Action dated July 21, 2016); *see also id.* at 168–174 (Office Action dated March 10, 2016).[12]

The applicant responded by: (1) amending the claims to specify that the combination therapy is administered orally, subcutaneously, or vaginally; (2) reiterating the argument and evidence related to unexpected results (citing, for example, data in Grant-2010, Garcia-Lerma, and the Specification's examples) raised during prosecution of the '509 patent; and (3) submitting a declaration from two of the inventors detailing further testing of the claimed combination therapy. Ex. 1004 (Amendment and Remarks dated Sept. 27, 2016), 34–36, 44–45, 49–52. The declaration provided survival curves (similar to Fig. 2 of the '191 patent, above) for different routes of administration of the combination therapy. *See, e.g.*, *Id.*

[12] The pending independent claims of the '887 Application at that time did not specify any particular route of administration for the combination of emtricitabine and tenofovir (or TDF). *See, e.g.*, Ex. 1004, 98 (claim 22).

at 50 (showing data for oral administration),[13] 51 (showing data for subcutaneous and vaginal administrations).

Shortly thereafter, the Examiner stated that the claims were allowable. Ex. 1004, 15–19 (Notice of Allowability), 20 (Summary of interview dated Oct. 6, 2016). The Examiner explained that the amendments, declaration, and remarks "have been entered and fully considered and found persuasive" and that applicants had provided evidence of "unexpected superior results residing in the claimed invention." *Id.* at 17–18.

II. ANALYSIS

A. *Principles of Law*

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")).

To show anticipation under 35 U.S.C. § 102, each and every claim element, arranged as in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir.

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[13] As the declaration explains, with oral monotherapies of TDF or FTC, between 75% and 70% of the macaques, respectively, became infected following multiple viral challenges whereas only 25% of the macaques administered combination FTC and TDF orally became infected. Ex. 1004, 50 ("Thus, the oral administration of TDF and FTC provide an unexpected superior effect.").

2008); *In re Chudik*, 851 F.3d 1365, 1372 (Fed. Cir. 2017) ("[A] prior art reference anticipates a claim only if it discloses all the elements in the same form and order as in the claim.") (internal quotation marks and citation omitted).

Turning to obviousness, a claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness when presented. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A party who petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted).

Moreover, objective indicia of non-obviousness (also known as secondary considerations) plays a key role in the obviousness inquiry and, among other things, guards against proscribed hindsight reasoning. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983);

Graham, 383 U.S. at 36 (holding that objective indicia "may also serve to guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue") (internal quotation marks and citation omitted).[14] Indeed, such evidence "may often be the most probative and cogent evidence in the record" and, accordingly, "must always when present be considered en route to a determination of obviousness." *Stratoflex*, 713 F.2d at 1538–39 (holding objective indicia evidence must "be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art").

B. *Person of Ordinary Skill in the Art*

In determining the level of skill in the art, we consider the problems encountered in the art, the art's solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Petitioner contends a person of ordinary skill in the art at the time of the invention would have

> been an individual familiar with the treatment and prophylaxis of HIV or similar viruses in individuals in a clinical and/or pre-

[14] "Obviousness requires a court to walk a tightrope blindfolded (to avoid hindsight)—an enterprise best pursued with the safety net of objective evidence." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012); *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075–80 (Fed. Cir. 2012) (holding that it is error to make an obviousness determination without considering objective indicia of nonobviousness in evidence).

> clinical setting. The knowledge held by such a person would have resulted from that person's education, training and experience, which would have included, for example, either an M.D. or an advanced degree in an allied field (e.g., microbiology, epidemiology, public health), along with 2–3 years of experience in those fields or in treating patients.

Pet. 16–17; Ex. 1009 ¶ 16. Patent Owner does not oppose this definition at this time. Prelim. Resp. 26.

Because Petitioner's proposed definition is unopposed and is not inconsistent with the cited prior art, we adopt it for the purposes of this Decision. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. *Claim Construction*

We interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b) (2019).[15] Under this standard, we construe

[15] The Office has changed the claim construction standard in AIA proceedings to replace the broadest reasonable interpretation standard with the same claim construction standard used in a civil action in federal district court. Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018). The change applies to petitions filed on or after November 13, 2018. *Id.* Because the present Petition was filed after that date, we construe the claims in accordance with the federal district court standard, now codified at 37 C.F.R. § 42.100(b).

the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.* "[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

1. *"protecting a primate host from a self-replicating infection"* (claims 1–12) / *"inhibiting establishment of a . . . self-replicating infection"* (claims 13–19)

The preamble of claim 1 recites "[a] *process of protecting a primate host from a self-replicating infection* by an immunodeficiency retrovirus." Ex. 1005, 12:32–47 (emphasis added). Similar language appears later in claim 1's body, which language recites "thereby protecting the primate host from infection with the immunodeficiency retrovirus." *Id.*

Petitioner argues that claim 1's preamble and related language in the body of the claim is not limiting. Pet. 20–21. According to Petitioner, this language is not necessary to give meaning to the claim, and merely conveys an intended and inherent result of practicing the "operative steps" of claim 1. *Id.* at 21–23. Petitioner reaches the same conclusion, based on substantially the same argument, with respect to claim 13's language reciting "inhibiting establishment of a . . . self-replicating infection." *Id.* at 23–24. So, Petitioner argues, "100% inhibition or prevention in any particular individual" is not required by the claims. *Id.*

Patent Owner counters that claims 1 and 13 "positively recite efficacy limitations" that should be given patentable weight. Prelim. Resp. 26–31. Patent Owner points out that the "protection" to which the claims are directed is, in fact, defined in the Specification.[16] *Id.* at 26–27, 30. Further, Patent Owner notes, the efficacy language appears not only in the preamble, but in the body of the claims. *Id.* at 28–30. According to Patent Owner, the efficacy language in the body of the claims is not "trivial" but was, instead, "introduced to overcome prior art rejections and explicitly reflect the claimed method's superior and unexpected results of preventing HIV infection in the face of great uncertainty and skepticism in the art." *Id.* at 30. Moreover, Patent Owner asserts, the recited efficacy language is not inherent in administering a combination of FTC and DTF to an uninfected person as Petitioner has elsewhere admitted. *Id.* at 30 (citing Petitioner's product label, which indicates that administering Truvada (FTC and DTF) is "not always effective in preventing acquisition of HIV-1"); Ex. 2002, 6. Thus, Patent Owner argues, the claims demand efficacy "by requiring the particular primate host, which received the claimed combination . . . prior to exposure, be HIV negative after exposure." Prelim. Resp. 29–30.

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[16] Patent Owner, similar to Petitioner, treats the "inhibiting the establishment" language of claim 13 as essentially equivalent to claim 1's "protecting" from infection language for purposes of addressing the claim construction issues presented in the Petition. Prelim. Resp. 27 ("So, like the 'protecting clause of Claim 1, 'inhbiting the establishment of a self-replicating infection' refers to the state of the patient (*i.e.*, being negative)."); *see also* Ex. 1009 ¶ 191 (Dr. Youle's testimony that "these phrases are referring to the same thing").

We start with the language of the claims, including the preamble. A claim's preamble is limiting when it is "necessary to give life, meaning, and vitality to the claim." *MBO Labs., Inc. v. Becton Dickinson & Co.*, 474 F.3d 1323, 1330 (Fed. Cir. 2007). As an initial matter, we observe that claim 1's step (a) recites "selecting a primate host not **infected** with **the** immunodeficiency retrovirus." Ex. 1005, 12:35–36 (emphases added). The "immunodeficiency retrovirus" in step (a), therefore, requires the preamble language for antecedent basis, and the preamble provides further meaning about the nature of the infection to which the claim is directed—"a self-replicating infection by an immunodeficiency retrovirus."[17] *Id.* at 12:32–33; *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003) ("When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention.").

Furthermore, the body of claims 1 and 13 requires, *inter alia*, administering "pharmaceutically effective amount[s]" of the combined agents. Without the preamble and other allegedly non-limiting portions of the claims, sufficient context for the "effective amount" language is lacking. Rather, these are amounts that can bring on the recited efficacy—in claim 1, "protecting" the host from infection. Otherwise the claims, focusing on the

[17] Reliance on the preamble also appears in claim 13. There, step (a) recites "selecting an *uninfected* human that does not have *the self-replicating infection*." Ex. 1005, 13:17–18 (emphasis added). This poses the question "uninfected" or an "infection" by what? That question, however, is first answered in the preamble, and later by the allegedly non-limiting "thereby" clause in the body of the claim.

"steps" alone might be understood as vaguely directed to administering agents to a subject in unspecified amounts for an indeterminate objective.

This is not a case, as in *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001), where "effective amount" language suggested no additional meaning nor implied any particular efficacy. There, the independent claims expressly included specific dosage information as material claim elements, which the court determined made the recited, intended result superfluous. *Id.* Not so with the claims here.[18] *Cf. Takeda Pharmaceutical Co., Ltd. v. Mylan Inc.*, 2014 WL 5862134, *8 (N.D. Cal. Nov. 11, 2014) (interpreting "effective amount" as referring to amounts effective in "treating reflux esophagitis"—a result recited in the claim); *see also id.* at *13 (discussing cases where "effective amount" language is interpreted as an amount necessary to produce certain efficacy); *Idenix Pharmaceuticals v. Gilead Sciences, Inc.*, 2018 WL 922125, *11 (D. Del. Feb. 16, 2018) (holding, in claim to "method for the treatment of a hepatitis C virus infection" that the preamble was limiting and "effective amount" means "an amount [of the recited compound] that is effective to treat HCV"). Accordingly, we conclude that the "protecting . . . from infection" and "inhibiting . . . infection" language provides necessary meaning to the inventions claimed, including the "effective amount"

[18] We recognize that some of the dependent claims (i.e., claim 12, and claim 18) do recite dosages for the agents. The independent claims, and most of the dependent claims, however, do not. There is no adequate basis here to limit the broader independent claims to subject matter appearing in only a few of the dependent claims.

language for the combination therapy appearing in the claim's body.

Contrary to Petitioner's intimation, there is no general rule that efficacy language in a claim is non-limiting. Whether such language should be given patentable weight turns on facts unique to each patent. *See, e.g.*, *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1373–76 (Fed. Cir. 2019) (affirming construction that result or efficacy language appearing in a wherein clause was limiting in light of the intrinsic evidence as a whole). Indeed, determining whether allegedly non-limiting language in a preamble or otherwise "involves examination of the entire patent record to determine what invention the patentee intended to define and protect." *Rowe v. Dror*, 112 F.3d 473, 478–80 (Fed. Cir. 1997); *Allergan*, 935 F.3d at 1374 (holding the court "must read the claims in view of the *entire* specification" and prosecution history) (internal quotation marks and citations omitted).

Moving beyond the claims themselves, based on the arguments and our review of the entire intrinsic record, we find that "protection" is at the heart of the invention described in the patent. The Specification is filled throughout with references—well over thirty—to "protection" (or roots or derivatives thereof), not to mention all the instances of like terms.[19] *See, e.g.*, Ex. 1005, Abstr. ("A process is provided for *protecting* a primate host from . . . infection . . . . *Protection* is achieved . . . . A regime . . . is also

[19] For example, the Specification describes a need for the invention because "society remains devoid of a preexposure prophylaxic regimen to *prevent* an individual from developing . . . infection subsequent to initial exposure," as well as a need for a "dosing regimen *effective in blocking* . . . infection." Ex. 1005, 2:2–10 (emphases added); *see also supra* Section I(C).

effective in providing *protection*."), 2:37–48 (describing a kit with a combination dose "sufficient to *protect* a primate host from developing a self-replicating retroviral infection"), 3:27–31 (disclosing that, through the combination therapy "prior to a retrovirus exposure *protection* is provided against . . . retroviral infection.") (emphases added). *Poly-Am., LP v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004) (holding that a specification "replete with references" to preamble language may show the inventor regarded the language as "an important characteristic of the claimed invention" and limit the claims). Further, as Patent Owner points out, "protection" is expressly defined in the Specification: it is "defined by the host primate being serologically negative and negative in response to a polymerase chain reaction (PCR) testing for the viral genome." Ex. 1005, 4:11–15; Prelim. Resp. 26–27, 30. ("Petitioner quotes the specification's definition, but does not adopt it."). The working examples also describe the nature and extent of the protection provided by the invention, to detail the invention and contrast the protection it provides versus monotherapies and no treatment. *See, e.g.*, Ex. 1005, 9:38–10:12; *Allergan*, 935 F.3d at 1375 ("[T]he specification demonstrates that [patent owner] believed the increased efficacy and safety of the claimed methods to be material to patentability."). The fact that "protecting" appears not once, but twice in claim 1, including in the body of the claim, is consistent with the import and repeated emphasis on protection in the patent overall.[20]

[20] Like the parties, we will generally treat the "inhibiting . . . infection" language of claim 13 similarly to the "protecting" language of claim 1 for purposes of this Decision. Pet. 23; Prelim. Resp. 27–28.

Moreover, "protection" was key in the patent's prosecution. As Patent Owner highlights, the efficacy limitations were added to the body of the claims (in the parent application) to overcome the Examiner's obviousness rejections. Ex. 1002, 103–120, 74–84. And the Examiner specifically relied on the protection (i.e., the "superior effect") provided by the invention in allowing the claims. *See, e.g.*, *id.* at 78, 81–82 ("As amended, the claims are drawn to the employment of particular combination of tenofovir and emtricitabine for protecting a primate . . . "). Indeed, the Examiner remarked that monotherapy with tenofovir prodrugs "has been shown as being *failed to protecting* animal from viral infection," yet "the claimed combination has clinically significant results [i.e., degree of protection], which would have not been expected in view [of] the prior art." Ex. 1002, 82 (emphasis added); Ex. 1006, 31–33 ("The claims are allowable for reasons as set forth in parent application"); *Allergan*, 935 F.3d at 1376–77 ("The prosecution history thus demonstrates that the formulation's efficacy and safety . . . were expressly relied on to define the claimed methods and distinguish them from the prior art."). Here again, we conclude that the intrinsic evidence, including the prosecution history, supports Patent Owner's position that the efficacy (e.g., "protecting . . . from infection") recited in the claims is material to patentability and limiting.[21]

[21] The result in *Bristol-Myers Squibb* (cited by Petitioner) is inapposite here. Pet. 21. In that case, the court considered numerous facts in determining that efficacy language in those claims was not limiting, facts that we are unpersuaded are applicable to the patent here. For example, the court cited patent owner's inconsistent positions on infringement (where it argued no

We are unpersuaded by Petitioner's argument that "protection" as claimed is necessarily inherent in administering any combination of NRTI and NtRTI. Pet. 22. The Specification does not support that conclusion. In fact, it suggests the opposite. For example, in the "Group 2" primates treated with a combination of FTC and DTF according to Examples 7 and 8, the patent discloses that "4 [of the 6 subjects] were protected," implying that two subjects were not protected. Ex. 1005, 9:54–56.[22] Moreover, as Patent Owner points out, Petitioner's own product labeling for Truvada (oral, fixed dose combinations of emtricitabine (200 mg) and tenofovir disoproxil fumarate (300 mg)) indicates that "TRUVADA is not always effective in preventing acquisition of HIV-1." Prelim. Resp. 30; Ex. 2002 (2018 Truvada Label), 6 (citing clinical studies and recommending "TRUVADA

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efficacy was required) and invalidity (where it argued efficacy was required), and remarked that patent owner "cannot have an expression be limiting in this context and non-limiting in another." *Bristol-Myers Squibb* 246 F.3d at 1375. The court also noted that, to the extent efficacy was raised in prosecution, it was limited to applicant's self-serving statements after the claims were allowed. *Id.*

[22] We agree with Petitioner, however, that "protection" may encompass a range of outcomes (Pet. 23), which likely depends at least partly on, for example, the testing employed and/or the number of viral exposures experienced. As the patent indicates, "[t]reatments of Groups 1-3 were all protective to a degree," with Group 1 including a monotherapy with FTC alone (and 2 of the 4 test subjects remaining uninfected at the conclusion of the testing). Ex. 1005, 9:48–51, 9:63–10:7. Under a different testing protocol (e.g., one with a lower number of viral exposures) it might be concluded that a different degree of protection was provided. For example, at week 8, none of the Group 2 subjects were seropositive for viral RNA. *See id.*, Fig. 2, 9:36–63 (describing infections as confirmed at weeks 10 and 12 in Group 2).

for HIV-1 PrEP only as part of a comprehensive prevention strategy that includes other prevention measures"). Accordingly, as asserted by Patent Owner, the evidence suggests "it is possible for a patient to take Truvada prior to exposure to HIV and still become HIV positive." Prelim. Resp. 30.

For the above reasons, we are unpersuaded by Petitioner's argument that the "protecting a primate host from self-replicating infection" and "inhibiting establishment of a . . . self-replicating infection" language of claims 1 and 13, respectively, are non-limiting. Pet. 20–24. Instead, as explained, we conclude that the efficacy language should be given patentable weight. For example, as argued by Patent Owner, claim 1 requires that the particular primate host receiving the claimed combination be protected—negative for infection with the immunodeficiency retrovirus (e.g., "HIV negative") after exposure. Prelim. Resp. 29.

2. "*self-replicating infection*" (claims 1 and 13)

According to Petitioner, "self-replicating infection" relates to "a point in time after an HIV exposure when the body's immune system alone cannot prevent progression of the HIV infection." Pet. 24 (citing 1009 ¶¶ 187–188). Petitioner asserts that this corresponds to a time about 72 hours after exposure "when infected CD4+ cells are being produced faster than the immune system can destroy them." *Id.* at 24–25; Ex. 1005, 1:45–49 (describing retroviral particles being transferred to an individual and "self-replicating" "within a few days"). Petitioner, thus, asserts that "self-replicating infection" means "an HIV infection that can no longer be suppressed solely by the host's immune system." Pet. 25 (italics omitted).

Patent Owner does not challenge Petitioner's interpretation of this phrase or offer an interpretation of its own. Prelim. Resp. 26–31.

It is not clear that further interpretation of this phrase is needed to resolve the dispute presented here. Nevertheless, Petitioner provides sufficient support for its interpretation on this record and, as it is unopposed at present by Patent Owner, we will adopt Petitioner's interpretation of this phrase for purposes of this Decision.

3. "*prior to the exposure*" (claim 1) / "*prior to a potential exposure*" (claim 13)

Petitioner contends that the claims use phrases, such as "prior to the exposure," to "specify when" the combined therapy is to be administered relative to the retroviral exposure. Pet. 25. According to Petitioner, "the exposure" need not be the *first* exposure, provided that, consistent with the requirement of the claims that the subject selected for the treatment be "not infected" or "uninfected," any "earlier exposure did not result in an HIV infection." Pet. 27; Ex. 1005, 12:35, 13:16. For claim 13, Petitioner contends that the phrase "a potential exposure" does not require that an "HIV exposure" "actually occur after administration of the antiretroviral agents." Pet. 27–28.

For the above reasons, Petitioner asserts that claims 1 and 13 encompass a process where the combination is "administered after an HIV exposure of the individual that did not result in an infection." Pet. 28. And, Petitioner asserts, claim 1, but not claim 13, "require[s] an administration to

precede an actual HIV exposure." *Id.*[23] Patent Owner does not contest Petitioner's assertions on the meaning of these phrases or offer its own interpretation. Prelim. Resp. 26–31.

Petitioner does not actually propose discrete constructions for these phrases, but rather has made assertions about what the language may require or encompass. Pet. 28. That said, Petitioner provides sufficient support for its assertions (presently unopposed). We conclude for purposes of this Decision that claim 1 requires an actual exposure to the immunodeficiency retrovirus, but note that it need not be the first such exposure with the proviso that the host is "not infected" for purposes of selection in accordance with claim 1's step (a). Ex. 1005, 12:35–36 ("(a) selecting a primate host not infected with the immunodeficiency retrovirus"). Claim 1 also requires, as asserted by Petitioner, the administration in step (b) occur "before a future [actual] exposure." Pet. 27. Claim 13 similarly requires "selecting an uninfected human that does not have the self-replicating infection," in its step (a) and, therefore, does not preclude selecting a human that may have been exposed to the immunodeficiency retrovirus at some earlier time so long as the earlier exposure did not result in infection. Ex. 1005, 13:16–17. And, the "administering" in claim 13 may precede an *actual* or a *possible* HIV exposure in the uninfected human. Pet. 27.

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[23] Petitioner notes that dependent claims 10 and 19 require administration both *before* and *after* exposure to the immunodeficiency retrovirus. Pet. 28. Claim 19, for example, recites: "The process of claim 17, wherein the tablet is administered daily for several days, weeks or months both before and after an exposure of the primate host to the immunodeficiency retrovirus." Ex. 1005, 14:22–25.

D. *Anticipation by Szekeres*

Petitioner asserts that claims 1–19 are unpatentable as anticipated by Szekeres. Pet. 33–51; *see id.* at 36–43 (independent claims 1 and 13), 43–51 (dependent claims).

We provide an overview of Szekeres, and then turn to analysis of the alleged anticipation.

1. Overview of Szekeres (Exhibit 1011)

Szekeres is a monograph on potential strategies for combatting HIV infection, including, in particular, pre-exposure prophylaxis ("PrEP") and whether PrEP might be effectively implemented for at-risk individuals in California. *See generally*, Ex. 1011, 1–3.

Szekeres discloses that "[p]re-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection." *Id.* at 1. PrEP, Szekeres explains, "should be distinguished from postexposure prophylaxis (PEP), in which an individual takes ARVs soon after a potential HIV exposure with the goal of reducing the likelihood of infection." *Id.* at 3.

According to Szekeres, "[i]t has been hypothesized that . . . PrEP could be a viable prevention strategy for certain people at high risk of HIV infection, such as commercial sex workers." *Id.* However, Szekeres explains, "[i]t is not yet known whether PrEP is a safe or effective approach to HIV prevention . . . as studies for its evaluation in several populations are just preparing to begin." *Id.* ("These planned studies and future, yet-to-be-planned clinical trials will determine whether and to what degree PrEP is

safe and effective."); *see also id.* at 6 ("Whether or not HIV PrEP will come to play as significant a role in HIV prevention as the use of ARVs for prevention of perinatal transmission . . . will largely depend on the outcome of current and future studies evaluating the safety and effectiveness of PrEP as an HIV prevention strategy.").

Szekeres describes ongoing and planned PrEP research to investigate its safety and/or efficacy in at-risk individuals. *See, e.g., id.* at 6–10. For example, Szekeres describes an ongoing study among men and women in certain countries in Africa, indicating that "[e]nrollment began in summer 2004" for the female participants, that the study is "to last approximately 2 years," and that the study's aims include evaluating the "safety" and "efficacy of TDF for PrEP." *Id.* at 7–8. In addition, Szekeres identifies a planned U.S.-based study of men who have sex with men (or "MSM"), evaluating "TDF for PrEP," and indicating that a 9-month recruitment of participants was "scheduled to begin in fall 2004," with the study expected to last 2 years. *Id.* at 7, 9 ("The CDC has plans to begin a randomized, double-blinded, placebo-controlled study of PrEP using TDF in high-risk, HIV-negative MSM in two cities in the United States in the fall of 2004."); *see also id.* at 9 ("This Phase II extended safety study will examine biological safety (clinical safety and tolerability) and behavioral safety (affect [sic] on risk behaviors), and as such will not include an evaluation of efficacy."). Szekeres further discloses that "[p]lanned studies of PrEP will screen for HIV infection prior to enrollment." *Id.* at 13. According to Szekeres, "[g]iven that these studies are still in the planning stages or have just recently begun . . . final data will likely not be available until mid-2006,

at the earliest." *Id.* at 9–10; *see also id.* at 12 ("How it would be determined whether PrEP use should be episodic or continuous, or for how long use of PrEP should continue for a given population or individual, are questions that are currently unanswerable and may or may not be clarified by currently planned studies.").

With respect to the studies, Szekeres discloses that they "are providing participants with 300 mg TDF tablets (or placebo) to be taken once daily during the study period." *Id.* at 12; *see also id.* at 8 ("These studies all make use of tenofovir disoproxil fumarate (TDF) as the investigational PrEP agent."). Indeed, as described in Szekeres, "[t]enofovir disoproxil fumarate (TDF) is the NRTI that is currently most suitable for use as PrEP." *Id.* at 11. Szekeres discloses, that "[i]t is important to note, however, that data on TDF safety to date have been from HIV-infected patients, and that unanticipated toxicities could result from chronic use of TDF in uninfected patients, as was the case with navirapine use for PEP." *Id.*; *see also id.* at 12 ("[I]t is hoped that the results of these studies will begin to shed light on the safety of using TDF for PrEP.").

Szekeres identifies a number of known antiretroviral drugs and formulations. According to Szekeres, "[t]here are currently 20 antiretroviral drugs approved for treating HIV infection in the United States," and "there are four fixed-dose formulations available that combine more than one drug into a single pill." *Id.* at 10. According to Szekeres, "[w]hile all of the available drugs could potentially provide some efficacy as PrEP, not all of them are ideal candidates." *Id.* at 10–11. Szekeres identifies several of these drugs, by category (e.g., "[p]rotease inhibitors," "[f]usion inhibitors,"

"NRTIs," etc.), and by name (e.g., "CCR5 antagonist UK 427,857," "nevirapine," "[l]amivudine (3TC)," "emtricitabine (FTC)," and "[t]enofovir disoproxil fumarate (TDF)"). *Id.* at 11. With respect to TDF, as noted above, Szekeres discloses that it "is the NRTI that is currently most suitable for use as PrEP" and "the investigational agent in the major PrEP studies." *Id.* Finally, Szekeres mentions Truvada, describing it, in full, as follows: "a once-daily, fixed-dose combination tablet of TDF and emtricitabine (Truvada™) was approved in August 2004 (both Gilead Sciences, Inc., Foster City, CA)." *Id.*

2. Analysis of Alleged Anticipation

Petitioner contends that Szekeres discloses a PrEP protocol and "identifies Truvada as one of two TDF-based drug products to use in PrEP." Pet. 33–34 (citing, e.g., Szekeres, 1, 3, 11). According to Petitioner, Szekeres further describes initiated or planned trials for evaluating PrEP, and poses "epidemiological questions" about PrEP's efficacy. *Id.* at 35. According to Petitioner, however, an ordinarily skilled person "would not have understood these epidemiological questions . . . as casting doubt that a PrEP regimen based on Truvada (TDF+FTC) would be effective in any individual who followed it properly." *Id.* at 35–36.

Turning to the claims, Petitioner addresses claims 1 and 13 together. Pet. 36–43. Petitioner contends that, although the preamble and "thereby" clauses in the body of the claims are allegedly "not limiting," Szekeres describes a process that "necessarily satisfies" that claim language. Pet. 35–36, 42–43 (arguing Szekeres "teaches administering Truvada to an HIV-uninfected individual before an HIV exposure, which results in oral

administration to that individual of the same 'pharmaceutically effective' amounts of TDF and FTC that the claims and the '191 Patent disclosure say will protect the host from an HIV infection").[24]

For the claimed "selecting" step, Petitioner contends that Szekeres "teaches administering antiretroviral agents to HIV-uninfected individuals," and discloses that potential subjects are "screened" and "must be confirmed to be HIV-negative before beginning PrEP." Pet. 37.

For the "administering" step and subsequent "wherein" clause, Petitioner contends Szekeres discloses administering antiretroviral agents to uninfected individuals prior to viral exposure. *Id.* at 37–38. Also, Petitioner contends, Szekeres identifies properties (e.g., daily dosing, favorable toxicity) of agents that may make them ideal PrEP agents. According to Petitioner, FTC has such properties, as does TDF. *Id.* at 39 (citing disclosure in Szekeres (Ex. 1011, 11) that "emtricitabine (FTC) cause[s] few toxicities and may be taken once daily, but . . . [is] susceptible to a single-point mutation at codon 184 that confers resistance, especially when taken alone"); *see also id.* at 40 (citing Ex. 1011, 11 (TDF "is the NRTI that is currently most suitable for use as PrEP")). Petitioner argues that Szekeres's teaching of potential resistance with FTC when used alone "would have been understood . . . as indicating FTC should be co-administered with another antiretroviral," such as TDF. *Id.* Then, Petitioner contends,

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[24] According to Petitioner, the dosages in Truvada (200 mg FTC and 300 mg TDF) are the same as amounts described in the patent. Pet. 42; Ex. 1005, 6:59–61 ("For an adult human, preferably each of the doses includes 200 mg of emtricitabine and 300 mg TDF.").

Szekeres "identifies Truvada as one of two TDF-based drug products that can be used in PrEP." *Id.*; Ex. 1011, 11 (describing "a once-daily, fixed-dose combination tablet of TDF and emtricitabine (Truvada™) [that] was approved in August 2004").

Citing Truvada's 2004 labeling, Petitioner contends that Truvada combines 200 mg of FTC and 300 mg TDF. Pet. 41–42; Ex. 1025, 21. Petitioner further asserts that the FDA-approved concentrations of the agents in Truvada would represent effective amounts based on the patent. *Id.* at 41. According to Petitioner, Truvada "will suppress HIV viral replication and exhibit potent antiviral activity" in a human and, thus, "not only effectively treats an HIV infection but prevents establishment of an HIV infection." Pet. 41 (citing, e.g., Ex. 1009 ¶¶ 92, 237, 242). Thus, Petitioner contends, step (b) of claims 1 and 13 (as well as the claimed "wherein" clauses) is described in Szekeres.

Patent Owner responds that Szekeres does not anticipate claim 1 (or claim 13) for at least two reasons. Prelim. Resp. 31–39. According to Patent Owner, Szekeres neither discloses step (b) nor the claimed efficacy. *Id.* Patent Owner contends that Szekeres is a "policy paper" exploring challenges with PrEP and "acknowledges that there was no successful HIV pre-exposure prophylaxis known in the prior art." *Id.* at 31 (citing Ex. 1011, 3). On step (b), Patent Owner contends that Szekeres discloses TDF as a monotherapy for PrEP, and that a single, tangential reference to Truvada does not rise to an anticipatory description of what is claimed. *Id.* at 31–35 ("The only approved use of Truvada at that time—and for nearly a decade thereafter—was for treatment of patients who were already HIV positive.").

On efficacy, Patent Owner contends that Petitioner's challenge is flawed for (i) interpreting the claims to delete any efficacy requirement, and (ii) failing to show that the claimed efficacy is expressly or inherently described in Szekeres. *Id.* at 35–38.

On whether the challenged claims are anticipated, we agree with Patent Owner on this record. Szekeres describes PrEP *monotherapy* using TDF as the agent. Indeed, that is the only agent Szekeres describes being used in the numerous ongoing PrEP studies/trials or even projected for use in PrEP studies planned for the future. Ex. 1011, 6–11 ("These studies all make use of tenofovir disoproxil fumarate (TDF) as the investigational PrEP agent."). And, even with respect to those studies, Szekeres expresses reservations as to whether TDF monotherapy, much less a combination therapy like claimed, would be safe or effective. *See id.* at 1 ("*If* PrEP proves to be safe and effective, numerous clinical questions will need to be resolved"), 3 ("It is *not yet known whether PrEP is a safe or effective approach* to HIV prevention."), 12 (describing questions about PrEP's use as "currently *unanswerable* and *may or may not be clarified* by currently planned studies") (emphases added). We are unpersuaded on this record that those reservations reflect only "epidemiological" issues or questions, and that they are inapplicable to whether PrEP would be seen as safe or effective in particular individuals following a course of treatment.

The brief, high-level mention in Szekeres of Truvada's FDA-approval does not sufficiently describe Truvada's use in a PrEP treatment that satisfies step (b) of the claims. Although claim language need not appear

ipsissimis verbis in the allegedly anticipating prior art,[25] the test remains one of "strict identity." *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002) (explaining that the "test for novelty" requires "strict identity"). When anticipation is the issue, close is not enough. *Jamesbury Corp. v. Litton Indus. Prods., Inc.*, 756 F.2d 1556, 1560 (Fed. Cir. 1985) (holding "anticipation is not shown by a prior art disclosure which is only 'substantially the same' as the claimed invention"), *overruled on other grounds, A.C. Aukerman Co. v. R.L. Chaides Constr. Co.*, 960 F.2d 1020 (Fed. Cir. 1992) (en banc). Indeed, "[a] prior art disclosure that 'almost'" discloses all the elements arranged exactly as in the claim, "may render the claim invalid under § 103, [but] it does not 'anticipate.'" *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (internal citation omitted). Petitioner's theory pieces together a host of disclosures, such as a potential for resistance with certain agents, and then filters and combines those disclosures based on what an ordinarily skilled person allegedly would have "understood" to ultimately conclude that Szekeres unambiguously describes PrEP combination therapy with Truvada. Pet. 38–42 (asserting that Szekeres "teaches orally administering Truvada in a tablet to an uninfected individual before an HIV exposure").[26] But Szekeres simply

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[25] *In re Schaumann*, 572 F.2d 312, 317 (CCPA 1978).

[26] For example, Petitioner argues that Szekeres's teaching of a potential for mutation and resistance with FTC monotherapy "would have been understood . . . as indicating FTC should be co-administered with another anti-retroviral." Pet. 39. From that, Petitioner contends Szekeres suggests FTC should be combined with DTC (the known agent actually being

does not describe in any adequate detail actual or prophetic use of Truvada in a PrEP regimen. To our eyes, Petitioner's theory invokes obviousness (if anything), not anticipation. *See Net MoneyIN*, 545 F.3d at 1371 (Fed. Cir. 2008) ("[D]ifferences between the prior art reference and a claimed invention, however slight, invoke the question of obviousness, not anticipation.").

We have also concluded that the preamble and thereby clauses include limiting language (e.g., "protecting . . . from infection") as explained above. *See supra* Section II(C)(1). Szekeres does not describe administering the claimed combination of agents (e.g., Truvada) and, unsurprisingly, provides no details about the efficacy of such a combination for PrEP. Prelim. Resp. 38. Such express details on efficacy would be missing in Szekeres even if we had agreed with Petitioner that use of Truvada in PrEP was sufficiently described or suggested in the reference.

As the efficacy language is entitled to patentable weight, without any express disclosure of efficacy of a combination therapy in Szekeres, Petitioner is left with inherency. We are, however, unpersuaded that inherency has been shown on this record. Petitioner's contention (Pet. 42) that Szekeres "necessarily" satisfies the claimed efficacy is unavailing because, based on the evidence here, it is possible (even if "unlikely") for an individual to receive combination therapy of FTC and DTF (or Truvada) and not be protected from infection. Prelim. Resp. 30, 36–37; *See, e.g.*,

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investigated in the PrEP studies described in Szekeres), with Truvada hence representing the combination of those therapeutic agents. *Id.* at 39–40.

Ex. 2002, 6 (describing Truvada as "not always effective" in protecting against HIV infection); *see supra* Section II(C)(1); *see also* Ex. 1011, 14 ("If PrEP is not 100% effective when used properly . . . then it is possible people may still seroconvert while taking PrEP."), 19 (PrEP "is unlikely to be 100% effective").[27] That possibility undermines inherency, which "may not be established by probabilities or possibilities." *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient" to show inherency). We are, thus, unpersuaded that Petitioner has demonstrated that Szekeres discloses, expressly or inherently, the claimed efficacy.

For the reasons above, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that claims 1 and 13 are unpatentable as anticipated by Szekeres.

The challenge to claims 2–12 and 14–19 depends on Petitioner first establishing that independent claims 1 and 13 are anticipated by Szekeres, and we are unpersuaded Petitioner's contentions on claims 2–12 and 14–19 make up for the deficiencies discussed above. Pet. 43–51; *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) ("It is axiomatic that a dependent claim cannot be broader than the claim from which it depends."). So, we also determine that Petitioner has not met its burden in

[27] Even if these disclosures of potential PrEP efficacy in Szekeres pertain to a "community" as Petitioner seems to suggest (Pet. 35–36), it would still not guarantee that PrEP would be effective in preventing infection in any particular individual. Such individual may be part of a subgroup for which treatment is not efficacious and protective against infection.

establishing a reasonable likelihood that it would prevail in establishing the challenged dependent claims are unpatentable under 35 U.S.C. § 102.

E. *Obviousness over Smith and Szekeres*

Petitioner asserts that claims 1–19 would have been obvious over Smith in combination with Szekeres. Pet. 51–79.

Szekeres is summarized above. *See supra* Section II(D)(1). We provide an overview of Smith below, followed by analysis of Petitioner's obviousness challenge.

1. Overview of Smith (Ex. 1012)

Smith is a publication related to recommendations from the U.S. Department of Health and Human Services on nonoccupational post-exposure prophylaxis (i.e., "nPEP") for HIV infection. *See generally*, Ex. 1012, 1–2 (Summary and Introduction).

Smith teaches that "[t]he provision of antiretroviral drugs to prevent HIV infection after unanticipated sexual or injection-drug-use exposure might be beneficial." *Id.* at 1 (italics omitted). Smith discloses:

> For persons seeking care ≤ 72 hours after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person known to be HIV infected, when that exposure represents a substantial risk for transmission, a 28-day course of highly active antiretroviral therapy (HAART) is recommended. Antiretroviral medications should be initiated as soon as possible after exposure.

Id. (italics omitted); *see also id.* at 8, Fig. 1. Pointing to data available from animal transmission models, Smith discloses that "[t]hese data indicate that nPEP might sometimes reduce the risk of HIV infection after

nonoccupational exposures." *Id.* at 2 (disclosing that "[a]nimal studies have demonstrated mixed results," citing, for example, "[t]wo macaque studies of combination antiretroviral therapy . . . initiated 4 hours after" viral challenge and continued for 28 days that "did not protect against infection but did result in reduced viral load among the animals infected."); *see also id.* at 13 ("Although nPEP might reduce the risk for HIV infection, it is not believed to be 100% effective.").

According to Smith, "[n]o evidence indicates that any specific antiretroviral medication or combination of medications is optimal for use as nPEP." *Id.* at 8 ("[E]vidence is insufficient to recommend a specific antiretroviral medication as most effective for nPEP."). Nevertheless, Smith teaches that, "on the basis of the degree of experience with individual agents in the treatment of HIV-infected persons, certain agents and combinations are preferred." *Id.* Smith teaches that "[p]referred regimens include efavirenz and lamivudine or emtricitabine with zidovudine or tenofovir (as a nonnucleoside-based regimen) and lopinavir/ritonavir . . . and zidovudine with either lamivudine or emtricitabine." *Id.* Moreover, Smith teaches that "[d]ifferent alternative regimens are possible (Table 2)." *Id.*

Smith's Table 2 identifies the following combination as one of its "[p]referred regimens": "Efavirenz[] plus (lamivudine or emtricitabine) plus (zidovudine or tenofovir)." *Id.* at 9 (Table 2). Smith's Table 3 identifies several additional HAART medications including "Emtricitabine/tenofovir (Truvada®)" and notes the adult dosage as "1 tablet once daily," which includes "200 mg emtricitabine/300 mg tenofovir." *Id.* at 10 (Table 3); *see also id.* at 8 ("One of the HAART combinations recommended for the

treatment of persons with established HIV infection should be selected on the basis of adherence, toxicity, and cost considerations (Tables 2 and 3).").

2. Analysis of Alleged Obviousness

Petitioner argues claims 1–19 would have been obvious. Pet. 51 (stating Patent Owner may argue Szekeres "does not describe the method of Claims 1 to 19, pointing to . . . [Szekeres's] observation that clinical trials to test its effectiveness were underway but not completed"). According to Petitioner, Szekeres would have provided a motivation "to modify the PEP regimen described in" Smith "by administering Truvada (TDF+FTC) to high-risk individuals before (rather than after) an actual HIV exposure." *Id.*

Petitioner contends that Smith suggests administering Truvada as part of PEP (post-exposure prophylaxis), and recommends PEP commence "as soon as possible" after exposure. *Id.* at 55–58; Ex. 1012, 1, 10. From this, Petitioner contends, the skilled person "would have recognized the theoretically optimal time to administer TDF+FTC to prevent HIV infection . . . would be several hours before an HIV exposure." Pet. 59. The only difference between Szekeres and Smith with respect to PEP and PrEP is, according to Petitioner, "timing." *Id.* at 59–61. Moreover, Petitioner contends, the skilled person would have been motivated to use Truvada based on its favorable side-effects profile compared to other antiretrovirals and to minimize resistance that can arise from monotherapies. *Id.* at 63–64.

Petitioner argues the ordinarily skilled person would have had a reasonable expectation of success in modifying Smith and Szekeres in this way to arrive at the claimed subject matter. Pet. 65–76. Petitioner contends

that PrEP would have been understood as an "optimal form" of PEP. *Id.* at 66–68. Also, Petitioner asserts, PEP and PrEP rely on the same mechanisms for purposes of suppressing infection. *Id.* at 68–69 ("The skilled person thus would have recognized that the way Truvada prevents HIV infection in the human body in the PEP regimen is identical to the way it does so in a PrEP regimen."). To the extent Smith or Szekeres allegedly express concerns about efficacy among a community, Petitioner argues that is not the salient issue because the claims do not require prevention in every individual. *Id.* at 70–72. According to Petitioner, "the relevant question for obviousness is whether a skilled person would reasonably believe that administering TDF+FTC to one uninfected individual will prevent establishment of an HIV infection in that individual." *Id.* at 72. And, in further support of the alleged reasonable expectation of success, Petitioner contends that HIV chemoprophylaxis was not highly unpredictable. *Id.* at 73–76 (citing, for example, disclosures in Subbarao (Ex. 1050) of "partial protection" with TDF monotherapy, and Grant-2006 (Ex. 1051) that "combinations of agents may be more suited for PrEP"); Ex. 1050, 904, 909; Ex. 1051, 875.

With respect to objective indicia of non-obviousness, Petitioner argues none exist. Pet. 76–79. According to Petitioner, there are no unexpected results because there is no nexus to the invention, and the results of using TDF+FTC in a PrEP regimen are simply attributable to practicing what was known in the prior art. *Id.* at 77 ("[A]t best, the '191 Patent provided simply a confirmation of what scientists knew and expected from the prior art."). Petitioner further contends there is no commercial success because, *inter alia*, it holds "blocking patents" to formulations of Truvada.

Id. at 77–78 (also asserting no skepticism or failure of others). In any event, Petitioner urges, "any evidence of secondary indicia advanced by Patent Owner in its response should be addressed after institution." *Id.* at 79.

Patent Owner contends that Petitioner's obviousness challenge should be rejected based on Petitioner's failure to address known objective evidence of non-obviousness. Prelim. Resp. 41–45. This evidence includes, according to Patent Owner, unexpected results evidence (e.g., Grant-2010 (Ex. 2004)) that persuaded the Examiner to allow the claims. *Id.* at 40–42. Patent Owner also argues that the combination of Smith and Szekeres does not teach all the claimed elements, that there is no sufficient motivation to administer the claimed combination for PrEP in light of those references, and that there is no reasonable expectation of success. *Id.* at 45–63; *see, e.g.*, *id.* at 52 (citing disclosure in Szekeres that "the K65R mutation in HIV-infected patients taking TDF in combination with other antiretroviral drugs has been seen with increasing frequency," thus discouraging a combination therapy like claimed). And, Patent Owner argues, substantial additional objective evidence shows that the claims are nonobvious. *Id.* at 63–67 (citing, for example, industry praise in various news sources, copying, and commercial success and licensing).

We construed the claims as requiring efficacy as discussed above. Section II(C)(1). Even considering Smith and Szekeres combined, we are unpersuaded of express disclosure of the claimed efficacy (i.e., "protecting the host from infection" as in claim 1) with FTC+TDF therapy in a PrEP regimen. Inherency too falls short. Evidence here suggests it is possible for particular individuals taking the combination of FTC+DTF (e.g., Truvada) to

become infected with HIV even when taking the combination. *See supra* Section II(C)(1), (D)(2).

On whether the ordinarily skilled person would have combined Smith and Szekeres to produce the claimed subject matter with a reasonable expectation of success, we have doubts on this record. From the prior art and other evidence here, a theme emerges. That is, while some of the evidence might indicate promise with TDF and TDF-combination therapies in PEP or PrEP, other (and sometimes the same) evidence casts doubts on whether those therapies would be safe or effective.

For example, Subbarao notes a "partial protection" with TDF monotherapy among the group of treated primates, but data show that only 1 of the 8 subjects receiving TDF remained uninfected. *See* Ex. 1050, 907 (Fig. 1, showing all 4 subjects receiving weekly administration became infected, and 3 of 4 receiving daily, oral administration became infected). Subbarao further explains that whatever delay in infection was seen was not statistically significant. *Id.* at 904, 909 (explaining, in 2006, that there "exists no precedent for giving chemoprophylaxis to large populations of people at risk for infection through repeated exposure to HIV"). Grant-2006 (cited by Petitioner) notes that Subbarao's model "set the bar much higher for chemoprophylaxis" and remarks that "[a]t the end of 14 weeks, all animals were infected." Ex. 1051, 874. According to Grant-2006, however, the "limited efficacy of TDF alone in highly stringent monkey models . . . raise the possibility that combinations of agents may be more suited to PrEP," and hypothesizes that Truvada might be a promising drug combination. *Id.* at 874–875. Yet, with respect to the then-ongoing

investigations with TDF, Grant-2006 explains that "[l]imited information about safety . . . may become available by the end of 2006, whereas information about efficacy is not expected until 2008-2009," and "[u]ntil then, PrEP is not recommended for clinical use." *Id.* at 875.

A similar pattern is present in Szekeres and Smith. For example, Szekeres discloses that "[a]lthough some guidelines exist for nonoccupational PEP, the safe and effective delivery of PEP remains complex, and reliable data on the use of PEP in settings in the United States is not available." Ex. 1011, 4. With respect to PrEP, Szekeres notes that studies investigating TDF's efficacy are "just beginning to get underway" and questions about how PrEP should be used were, at that time, "unanswerable." *Id.* at 12, 23 ("Ultimately, however, data from planned PrEP studies will be needed before it can be determined for whom PrEP is an appropriate strategy."). On the other hand, Szekeres discloses that "models" about the potential impact in California "indicate that introduction of PrEP may quickly reduce incidence, with effects on prevalence being less dramatic and over a longer period of time." *Id.* at 1; *see also id.* at 11–12 ("As prescription medicines go—and HIV drugs in particular—TDF appears to be a relatively safe agent with few adverse side effects and interactions with other drugs."). Smith teaches, for example, that "data indicate that nPEP might sometimes reduce the risk of HIV infection," but also discloses that "[a]nimal studies have demonstrated mixed results," that "[a]ntiretriviral PEP does not prevent all infections" and "PEP failures have been documented," and "[b]ecause nPEP is not 100% effective in preventing transmission" and carries risks for "serious toxicities, nPEP should be used

only for infrequent exposures." Ex. 1012, 2, 5, 6 (disclosing that persons who engage in conduct "that result[s] in frequent, recurrent exposures . . . should not take nPEP").

All that said, even if we agreed for purposes of institution that Petitioner had shown that all the claim elements were taught (expressly or inherently[28]) in the prior art, and shown a sufficient reasonable expectation of success, there remain problems with the present Petition. Specifically, the Petition fails to grapple persuasively with developed, and *well-known* evidence of unexpected results in the prosecution record. As explained above, this evidence was key to the allowance of the claims despite the Examiner's determination that the claimed subject matter was otherwise taught or suggested in the prior art. *See supra* Section I(E); *Stryker Corp. v. KFX Med., LLC*, IPR2019-00817, Paper 10 at 28–29 (PTAB Sept. 16, 2019) ("We have cautioned petitioners in prior proceedings that petitions may be denied if they do not address known evidence of secondary considerations.").

The Petition provides no sufficient rebuttal to the actual results exhibited with the claimed combination as evidenced in, at minimum, the Specification's examples or Grant-2010 (Ex. 2004) to explain why those results would have been expected. As discussed above, the patent itself, buttressed by a paper in the scientific literature by Garcia-Lerma, evidences

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[28] *Honeywell Int'l Inc. v. Mexichem Amanco Holdings S.A. DE C.V.*, 865 F.3d 1348, 1355 (Fed. Cir. 2017) (explaining that, even if features of the invention are inherent, they may be "unexpected" and evidence nonobviousness).

a "7.8-fold" reduction in infection with combined FTC+DTF therapy, including against multiple viral challenges. *Supra* Section I(E); Ex. 1005, 9:54–59; Ex. 1155, 1, 5; *see also* Ex. 1002, 119 (describing a 16.7-fold reduced risk of infection as evidenced by another technical publication). Grant-2010 details a clinical trial demonstrating further results with the claimed method—at least a 92% reduction in HIV infection. Ex. 2004, 2596–2597; Prelim. Resp. 18 (noting that "Grant-2010 describes the results of the first clinical (i.e., human) study—known as iPrEx—demonstrating the effectiveness of Patent Owner's claimed method"), 41–42.

For the Examiner, this evidence was decisive in overcoming the obviousness rejections of the claims in the '191 patent and its ancestral applications. Ex. 1006, 33; Ex. 1002, 78 (citing the "unexpected results shown in the application and exhibits. Particularly, [the] Grant reference."); *see also id.* at 81–82 (finding the "application shows that the combination has superior effect . . . and evidences on the record has shown the claimed combination has clinically significant results, which would have not been expected."); *see also* Ex. 1004, 15–19. It is also facially persuasive evidence of nonobviousness here, especially without a direct and persuasive rebuttal from Petitioner.[29]

[29] Petitioner cites to other papers from Grant ("Grant-2006," Ex. 1051; "Grant-2005," Ex. 1053). Pet. 74. But those papers do not report the results of the studies in Grant-2010 (Ex. 2004), and Petitioner does not address those results directly to explain why they would have been expected. Petitioner also cites an exhibit it describes as "Grant-Proposal" (Ex. 1135). Pet. 78. But this exhibit is an email chain, attaching a "Confidential"

This evidence of unexpected results is part of the public prosecution of the patent and, on this record, Petitioner should have addressed those results head-on in the Petition, particularly in view of the pivotal role they played in securing allowance of the claims. *See Coalition for Affordable Drugs V LLC, v. Hoffman La-Roche Inc.*, IPR2015-01792, Paper 14 at 17–18 (PTAB Mar. 11, 2016) (denying institution due, in part, to petitioner not addressing the objective indicia of nonobviousness relied upon by the examiner); *see also Merial Limited v. Virbac*, IPR2014-01279, Paper 13 at 27 (PTAB Jan. 22, 2015) (concluding petitioner "was aware of the unexpected results showing which the Examiner found persuasive . . . [and petitioner] should have addressed the unexpected results in the first instance."). Patent Owner also persuades us that Petitioner knew of, indeed relied upon, those results in the past. Prelim. Resp. 41–42; Ex. 2025 (2012 Truvada label), 32–34 ("The iPrEx study and Partners PrEP study support the use of TRUVADA to help reduce the risk of acquiring HIV-1"). Under these circumstances, we find that Petitioner's failure to persuasively address the results in its Petition means Petitioner falls short of its burden to establish a reasonable likelihood of success in prevailing on its challenge.

Petitioner's vague assertions about the results being attributable to the prior art and a lack of a nexus are an insufficient response to the concrete unexpected results evidence here. Pet. 76–77. The Board sometimes puts

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concept sheet about a proposed study on Truvada. Ex. 1135, 1–6. Petitioner does not assert, and it is not evident, that this exhibit demonstrates that the results reported in Grant-2010 would have been expected to the ordinarily skilled person.

off until trial exploration into, and conclusions on, alleged objective indicia of nonobviousness, especially when the objective indicia are raised for the first time in a patent owner's preliminary response, and a petitioner has no reasonable *a priori* notice of such evidence or argument. That might be an appropriate approach to deal with, for example, Patent Owner's assertions of industry praise or copying at the institution stage. Prelim. Resp. 64–65. But the same cannot be said for the specific evidence of unexpected results that prompted allowance of the '191 patent's claims, evidence that came up again and again during prosecution of the family of patents challenged by Petitioner as the basis for why the claims were allowed.

For the reasons explained above, we determine the Petition has not established a reasonable likelihood that Petitioner would prevail in showing that claims 1 and 13 are unpatentable as obvious over Smith and Szekeres.

The challenge to claims 2–12 and 14–19 depends on Petitioner first establishing that independent claims 1 and 13 would have been obvious over Smith and Szekeres, and we are unpersuaded Petitioner's contentions on claims 2–12 and 14–19 make up for the deficiencies in Petitioner's analysis and evidence discussed above.[30] So, we further determine that Petitioner has not met its burden in establishing a reasonable likelihood that it would prevail in establishing the challenged dependent claims are unpatentable under 35 U.S.C. § 103.

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[30] Petitioner does not provide separate argument or analysis for the dependent claims specific to its obviousness challenge, but we have considered (for purposes here), Petitioner's contentions about the dependent claims relative to the anticipation challenge.

F. *Discretionary Denial Under § 325(d)*

Patent Owner contends that we should exercise our discretion under 35 U.S.C. § 325(d) to deny *inter partes* review in this case. Prelim. Resp. 19–26. Specifically, Patent Owner argues, *inter alia*, that the Examiner evaluated the same prior art asserted by Petitioner here—Szekeres and Smith—during prosecution of the '191 patent and issued a rejection of the then-pending claims for obviousness over Szekeres and Smith in combination with a handful of other references. *Id.*

Petitioner urges us to reject Patent Owner's arguments for discretionary denial. According to Petitioner, it presents different grounds (e.g., anticipation) and evidence (e.g., the Youle Declaration) in support of its grounds than what was considered by the Examiner. Pet. 79–80. Moreover, Petitioner contends, the Examiner erred in their evaluation of Szekeres and Smith. *Id.* at 80–83; *see supra*, Section I(E); *see also* Paper 14, 1–5 (arguing, *inter alia*, that Patent Owner's statutory disclaimer of certain claims in the '509 and '333 patents and "error" by the Examiner undermine arguments for § 325(d) discretionary denial).[31]

[31] Petitioner's argument in its Reply treats the disclaimer as a concession by Patent Owner that the disclaimed subject matter is unpatentable. *See, e.g.*, Paper 14, 3 (citing "Patent Owner's tacit admission of the unpatentability of the disclaimed claims"). But, as Patent Owner points out, "[s]tatutorily dismissed claims are not admissions of unpatentability." Paper 15, 1, 2 (explaining that Patent Owner disclaimed certain claims of the '509 and '333 patents to focus on claims unambiguously directed to PrEP). Petitioner has provided no persuasive authority in support of its position concerning the disclaimers. We agree that 37 C.F.R. § 42.73(b) and (d), and *Comcast Cable*

Rather than deciding whether the Petition should be denied under 35 U.S.C. § 325(d), we conclude that it is more appropriate on this record to resolve our decision on institution based on the merits of Petitioner's challenge to the claims. Because, as noted above, we find that Petitioner has not met its burden to establish a reasonable likelihood of prevailing on the grounds asserted here, we deny institution, and decline to decide whether institution should be denied on a discretionary basis under § 325(d).

III. CONCLUSION

On this record, for the reasons provided above, Petitioner has not established a reasonable likelihood of prevailing on its assertion that at least one of the challenged claims is unpatentable based on the grounds advanced.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied, and we do not institute *inter partes* review of any claim of the '191 patent based on the grounds asserted in this Petition.

Comms. LLC v. Rovi Guides, Inc., IPR2019-00224, Paper 14 (PTAB June 3, 2019) are not applicable to the present case based on the reasons given by Patent Owner. *Id.* at 3–4, n.2.

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