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# Tuberculin Skin Test Negativity Is Under Tight Genetic Control of Chromosomal Region 11p14-15 in Settings With Different Tuberculosis Endemicities

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**A substantial proportion of subjects exposed to a contagious tuberculosis case display lack of tuberculin skin test (TST) reactivity. We previously mapped a major locus (*TST1*) controlling lack of TST reactivity in families from an area in South Africa where tuberculosis is hyperendemic. Here, we conducted a household tuberculosis contact study in a French area where the endemicity of tuberculosis is low. A genome-wide analysis of TST negativity identified a significant linkage signal ( $P < 3 \times 10^{-5}$ ) in close vicinity of *TST1*. Combined analysis of the 2 samples increased evidence of linkage ( $P = 2.4 \times 10^{-6}$ ), further implicating genetic factors located on 11p14-15. This region overlaps the *TNFI* locus controlling mycobacteria-driven tumor necrosis factor  $\alpha$  production.**

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**Keywords.** tuberculosis infection; tuberculin skin test; genome-wide linkage; human genetics.

*Mycobacterium tuberculosis* is the main cause of human tuberculosis, a disease that remains a major public health concern worldwide. Despite the widespread use of BCG vaccine and specific control programs based on combinations of potent antibiotics, tuberculosis kills more individuals per year than any other infectious agent. Progression to clinical tuberculosis is far from inevitable, as only an estimated 10% of individuals infected by *M. tuberculosis* develop clinical disease [1], whether during primary infection or later in life by reactivation of latent or secondary infection. There is accumulating evidence that human genetics play an important role in explaining this large clinical variability [1–3].

There is also interindividual variability at an earlier stage of the infectious process, as approximately 30%–50% of subjects with heavy exposure to *M. tuberculosis* in household studies do not become infected [4]. This estimate is based on the diagnosis of *M. tuberculosis*-infected and uninfected persons by means of the tuberculin skin test (TST), which measures induration on the skin after intradermal inoculation of tuberculin (ie, *M. tuberculosis* purified protein derivative). Several family studies have provided consistent evidence for an important role of human genetics in the control of *M. tuberculosis* infection or TST reactivity [5, 6]. Indeed, by focusing on TST negativity (TST induration diameter, 0 mm vs >0 mm) in an area hyperendemic for tuberculosis in South Africa, we recently mapped *TST1*, located on chromosomal region 11p14, as a major locus controlling this phenotype [7].

We report here results of a genome-wide linkage analysis (GWLA) of TST negativity in a household tuberculosis contact study conducted in a suburb of Paris, France. We identified a significant linkage signal ( $P$  value, approximately  $2 \times 10^{-5}$ ) in close vicinity of *TST1*. Combined analysis of the French and South African samples increased evidence of linkage at the *TST1* locus ( $P$  value, approximately  $2 \times 10^{-6}$ ), consistent with the hypothesis that *TST1* is a major locus controlling TST negativity.

## MATERIAL AND METHODS

A prospective study of household tuberculosis contacts was conducted in the Val-de-Marne suburb of Paris, as detailed in [8]. Briefly, Val-de-Marne is an area of low tuberculosis endemicity with an annual tuberculosis incidence of 22.1 cases per

100 000 inhabitants. From April 2004 to January 2009, household contacts exposed to a patient with culture-confirmed pulmonary tuberculosis were enrolled in the context of a general screening procedure. A household contact was defined as any person sharing the residence of a tuberculosis index case during the 3 months preceding diagnosis of the case. The first screening visit (V1) included clinical examination, performance of a TST (ie, intradermal injection of 0.1 mL [5 tuberculin units] of tuberculin obtained from a human-pathogenic *M. tuberculosis* strain [Tubertest; Sanofi Pasteur, Lyons, France]), chest radiography, and a completion of standardized questionnaire to assess risk factors of *M. tuberculosis* infection, as detailed elsewhere [8]. These investigations were repeated 8–12 weeks later (V2) in household contacts for whom no infection was diagnosed at V1 [8].

We dichotomized the TST distribution, using a 0-mm induration as the threshold, to define a binary TST status (TST-bin). Individuals with a discordant TST-bin status between V1 and V2 were excluded. Prior to linkage analysis, we assessed the effect of relevant covariates on TST-bin by determining the infectivity of the index case, based on the presence of cavitation on chest radiography or the presence of bacilli in sputum smears, age, sex, and estimated total exposure of the contact to the index case (quantified as the number of days the contact spent with the index case during the 3 months preceding the diagnosis of tuberculosis). To account for the relatedness of individuals, the impact of these covariates was assessed by estimating equation methods, as implemented in the R package GEEPACK (<http://cran.r-project.org/web/packages/geepack/index.html>), using a logit link function and an identity working correlation matrix.

Genotyping of children and parents for the GWLA was performed at the Centre National de Génotypage (Paris) with the Illumina linkage V panel. Nonpolymorphic single-nucleotide polymorphisms (SNPs) and SNPs with a call rate of <90% were removed from the analysis. Linkage analysis was performed on the quantitative Pearson residuals, obtained by adjustment of TST-bin on sex, age, level of exposure, and index case infectivity. Model-free GWLA was performed by means of the new maximum-likelihood binomial (MLB) method for quantitative traits (nMLB-QTL v.3.0) [9, 10]. The MLB approach considers the sibship as a whole and does not make any assumption about the distribution of the phenotype. The test of linkage is a maximum-likelihood ratio test asymptotically distributed as a 50:50 mixture of  $\chi^2$  distributions with 0 and 1 degree of freedom and can be expressed as a classic LOD score. We used LOD scores of 3.6 and 2.2 as genome-wide significant and suggestive thresholds, respectively, as described in [7].

## RESULTS AND DISCUSSION

First, the analysis of covariates in the French cohort was performed on 540 household tuberculosis contacts belonging to

155 pedigrees. Among them, 84 (15.6%) had a TST induration size of 0 mm at both visits and were classified as having a negative TST-bin. The mean age ( $\pm$ SD) at the time of TST was  $24.1 \pm 18.0$  years, and the male to female ratio was 1.05. BCG vaccine coverage was very high, with 13 individuals (2.6%) not vaccinated with BCG vaccine. The mean duration of exposure to the index case ( $\pm$ SD) was  $19.25 \pm 21.6$  days, and 449 household contacts (83.1%) were exposed to an index case presenting cavitation on chest radiography or bacilli in sputum smears. Univariate and multivariate (ie, testing all covariates simultaneously) analysis showed that age had the strongest impact on TST positivity (Table 1). Index case infectivity and total exposure time to the index case were also significantly associated with a positive TST result (Table 1).

Second, from the French sample, 97 nuclear families, including 237 offspring, were informative for linkage analysis (ie, composed of at least 2 genotyped sibs with a TST value). Characteristics of the 237 offspring are shown in [Supplementary Table 1](#). Among them, only 4 had not received BCG vaccine, eliminating BCG vaccination as a potential confounding factor in our study. Results of the GWLA of TST-bin adjusted on the covariates are presented in Figure 1A. Information content was high across all autosomes, with mean genome-wide information of approximately 90%. We identified 1 major locus, at position 14.3 Mb on chromosomal region 11p15, that reached the threshold commonly used to claim genome-wide significance (LOD score, 3.65;  $P = 2.08 \times 10^{-5}$ ; Figure 1A). In addition, we identified 18 weaker linkage peaks with a  $P$  value of <.01 ([Supplementary Table 2](#)).

This major locus mapped at approximately 12 Mb from the *TST1* locus previously identified as controlling TST negativity in South Africa [7]. Considering the precision of location estimates in linkage studies of complex traits [11], this result is consistent with replication of the South African *TST1* locus in the French cohort. We therefore refined the linkage signal at chromosomal region 11p14-15 by performing a GWLA on the pooled samples (Figure 1B). Evidence of linkage for TST-bin increased in the analysis of the combined sample, compared with the analysis of each sample separately (Figure 1A; [7]), with a maximum LOD score of 4.54 at position 23.44 Mb ( $P = 2.40 \times 10^{-6}$ ; Figure 1C). This linkage peak was preceded by a plateau from 11 to 20 Mb with LOD scores varying between 2.5 and 2.8. It is therefore difficult to precisely define the bounds of the confidence interval for the true location of *TST1*. Of note, we also observed suggestive evidence of linkage in the combined sample on chromosomal region 19q13 (LOD score, 2.85 at position 55.55 Mb), whereas only moderate evidence of linkage was observed in the analysis of each sample separately.

To further explore and refine the region of interest on chromosome 11p14-15, we restricted our analysis to French and South African families showing evidence of linkage (ie, those with a LOD score of >0) in the region extending from 10 Mb

**Table 1. Impact of Covariates on the Risk of Having a Tuberculin Skin Test (TST) Induration of >0 mm Among 540 Household Tuberculosis Contacts**

Covariates	TST Induration >0 mm, No. (%)	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	P Value	OR (95% CI)	P Value
<b>Sex</b>					
Male	235 (84.8)	...		...	
Female	221 (84.0)	0.94 (.62–1.43)	.77	0.85 (.54–1.35)	.49
<b>Age,<sup>a</sup> y, range (reference point)</b>					
			$2.5 \times 10^{-10}$		$7.9 \times 10^{-9}$
0–10 (5)	113 (69.3)	...		...	
10–20 (15)	91 (91.2)	2.80 (2.07–3.78)		2.94 (2.11–4.12)	
20–30 (25)	80 (92.5)	4.31 (2.86–6.49)		4.60 (2.91–7.28)	
>30 (40)	186 (90.3)	4.54 (2.84–7.27)		4.76 (2.81–8.07)	
<b>Exposure duration,<sup>a</sup> d, range (reference point)</b>					
			.027		.04
0–3 (1)	133 (78.7)	...		...	
3–15 (7)	131 (90.3)	1.45 (1.10–1.91)		1.52 (1.13–2.04)	
>15 (30)	190 (85.2)	1.98 (1.10–3.58)		2.45 (1.29–4.65)	
<b>Index case infectivity<sup>b</sup></b>					
No	64 (71.9)	...		...	
Yes	390 (86.9)	2.58 (1.47–4.53)	.001	3.20 (1.82–5.64)	$5.8 \times 10^{-5}$

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup> Effect of continuous variables age and exposure was modeled using fractional polynomials (FP) as described elsewhere [7, 8]. For each variable, first degree (FP1) and second degree (FP2) FP models were fitted with power p for FP1 and p and q for FP2 chosen from –2, –1, –0.5, 0, 0.5, 1, 2, and 3, with 0 denoting log transformation. Among the 44 possible combinations, the model providing the smaller Akaike information criterion was selected. FP2 models with p = 1 and q = 1 and p = 0.5 and q = 2 were selected for age and exposure, respectively. For interpretability, category-based estimates are replaced with those from the regression model at relevant age and exposure length.

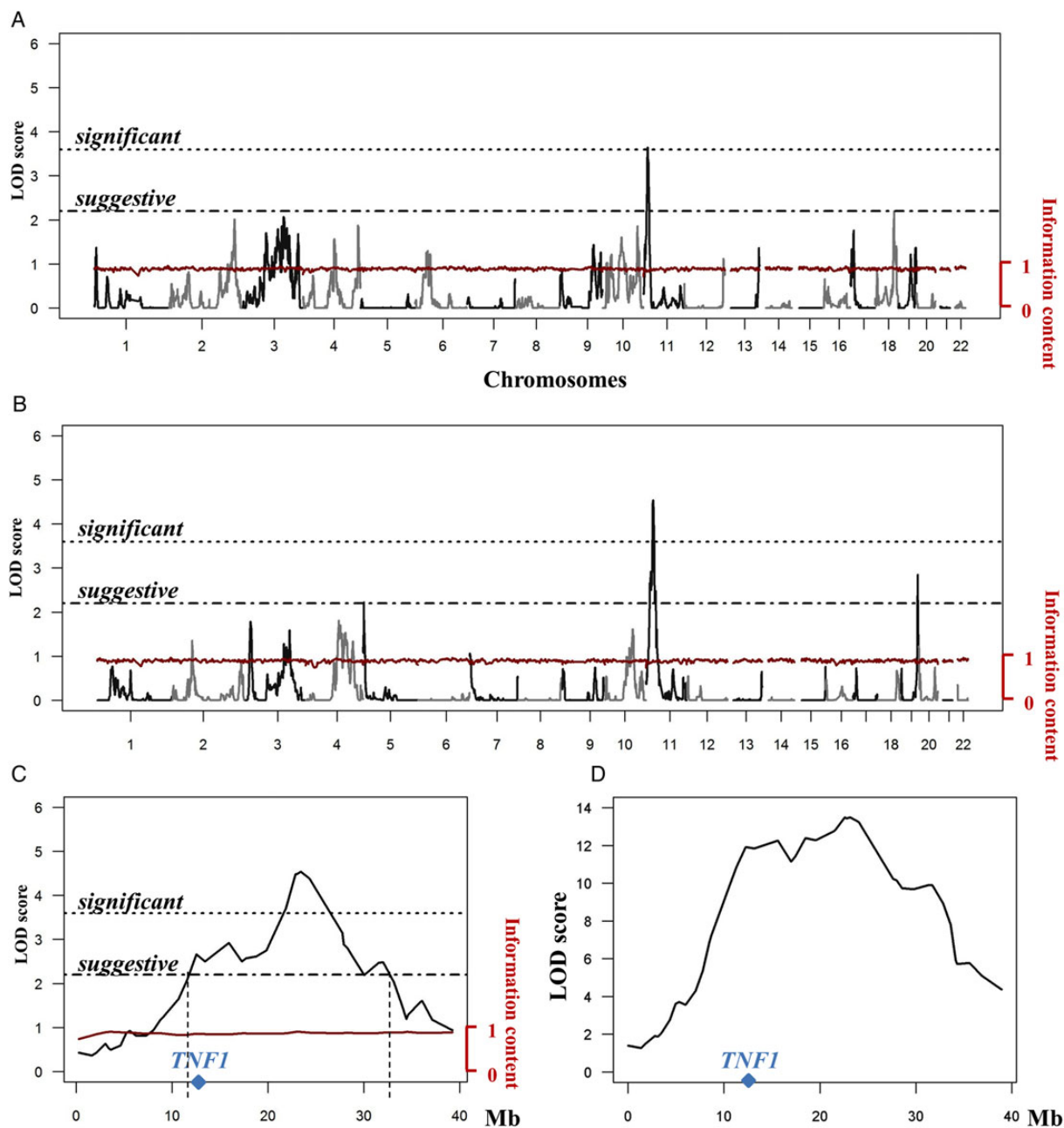
<sup>b</sup> Defined as cavitation on the chest radiograph or bacillary in sputum smears.

to 34 Mb. Our goal was to narrow the size of the region of interest by removing the noise randomly generated by unlinked families (eg, because of genetic heterogeneity). Results are shown in Figure 1D. While the height of the linkage peak has no more formal interpretation in that situation, its shape shows that the plateau observed between 11 and 20 Mb in Figure 1C is likely part of the region of interest. This region of interest, defined as displaying a LOD score of >2.2 in Figure 1C, extends from 11.6 Mb to 33.1 Mb and contains 194 genes (Supplementary Table 3). Of note, *WT1* located at 32.4 Mb is the closest gene to rs2057178, a SNP found to be associated with pulmonary tuberculosis in several genome-wide association studies performed in different populations [12, 13]. Identification of genetic variant(s) underlying the linkage peak is ongoing following the same strategy (based on ultra-fine linkage disequilibrium mapping) as the one successfully used for pulmonary tuberculosis [3].

While the phenotype of interest was similar in the South African and French samples (ie, TST negativity, defined using a stringent cutoff of a 0-mm induration), the 2 studies were otherwise remarkably different. The South African study took place in an area hyperendemic for tuberculosis [7], where the transmission of *M. tuberculosis* occurs preferentially in the community, and with no requirement for the enrolled individuals to be household contacts of tuberculosis cases. By contrast, France is

a country with low tuberculosis endemicity, and the study design was a household tuberculosis contact study, which enabled us to take into account and quantify both the level of exposure and the index case infectivity. Beside the exposure context, the 2 studies also differed in terms of genetic background, as captured by the difference in ethnicities of subjects in each study. All the individuals studied in [7] belonged to the South African Coloured ethnic group, a unique highly admixed population resulting from the encounter of different founders from Africa, Europe, and Asia. By contrast, individuals in the present study belonged to several ethnic groups (white [48%], African [33%], Asian [6%], and mixed and other [13%]). Thus, replication of *TST1* in such different settings suggests an important role of this locus in the control of TST negativity in humans.

The risk of developing tuberculosis for immunocompetent persons without TST reactivity despite sustained exposure to *M. tuberculosis* was previously shown to be extremely small [14]. Thus, persons with a TST induration of 0 mm are more likely not infected by *M. tuberculosis* than intrinsically deficient in mounting a delayed type hypersensitivity response. In the French cohort, the individual level of exposure to *M. tuberculosis* was variable. Some individuals were constantly exposed to a highly infectious case and are very likely naturally resistant to *M. tuberculosis* infection. Others were occasionally exposed to a moderately infectious case, and in this instance it is not



**Figure 1.** Genome-wide model-free linkage analysis of tuberculin skin test negativity (TST induration diameter, 0 mm vs >0 mm) in the French (A) and the combined French and South-African samples (B). Multipoint evidence of linkage expressed as a classical LOD score (black line; left y-axis) and the information content (red line; right y-axis) are plotted along the 22 autosomes. The 2 dotted horizontal lines indicate the formal cutoffs for genome-wide suggestive or significant linkage. C, Expanded view of the region with the highest LOD score in the combined analysis (y-axis) along chromosome 11 from 0 to 40 Mb (x-axis). The multipoint evidence of linkage (black line) and information content at marker positions (red line) are given. Left and right y-axes indicate the LOD score and information content, respectively. A blue diamond indicates the *TNF1* locus position. D, Multipoint evidence of linkage in the combined sample restricted to 114 families contributing to the linkage peak on 11p14-15. A family was considered as contributing positively to the linkage peak when the maximal positive LOD score contribution was greater than the absolute value of the maximal negative LOD score contribution within the 10–33-Mb interval on chromosome 11. A blue diamond indicates the *TNF1* locus position. Abbreviation: TNF, tumor necrosis factor.

possible to distinguish between lack of exposure and resistance to infection. However, since lack of exposure is difficult to reconcile with a genetic cause, the most parsimonious

explanation is that the 11p14-15 locus reflects an innate mechanism of resistance to *M. tuberculosis* infection. Such a mechanism is an attractive working avenue for prevention as it could

be an efficient target to protect persons from infection with highly drug resistant *M. tuberculosis* strains or those with a weakened acquired immunity arm, such as human immunodeficiency virus-infected subjects.

Interestingly, the major locus at chromosomal region 11p14-15 overlaps the *TNF1* locus identified for mycobacteria-driven tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) production by leukocytes in the South African family sample (Figure 1C and 1D) [15]. TNF is a key effector molecule of tuberculosis resistance that is critical for the sequestration of *M. tuberculosis* in infectious granuloma during latent *M. tuberculosis* infection [1]. Hence, the overlap of *TST1* with *TNF1* provides additional support for the interpretation of the *TST1* locus as conferring resistance to *M. tuberculosis* infection. In addition, the observation that the suggestive locus on chromosomal region 19q13 mapped in the vicinity of a locus also found to be linked to TNF production in the South African family sample ( $P < .01$  from 58.1 to 59.1 Mb [15]) reinforces the hypothesis of a genetic connection between TST negativity and TNF production.

## Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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RANDOMISED CONTROLLED TRIALS

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REAL-WORLD EVIDENCE

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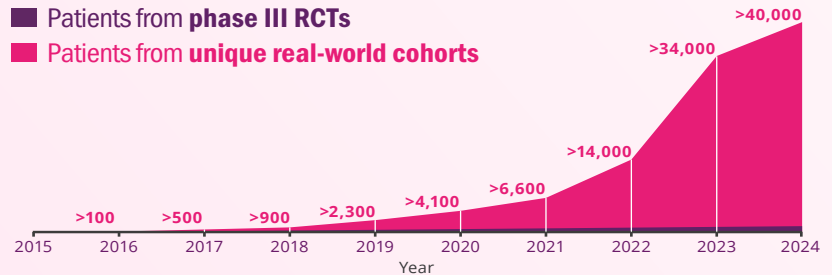
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### ABBREVIATIONS

**3TC**, lamivudine; **CD4**, cluster of differentiation 4; **DTG**, dolutegravir; **FDA**, United States Food and Drug Administration; **FTC**, emtricitabine; **HIV**, human immunodeficiency virus; **ITT-E**, intention-to-treat exposed; **NRTI**, nucleoside/nucleotide reverse transcriptase inhibitor; **RCT**, randomised controlled trial; **RNA**, ribonucleic acid; **TAF**, tenofovir alafenamide fumarate; **TDF**, tenofovir disoproxil fumarate; **XTC**, emtricitabine.

### FOOTNOTES

\*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

\*\*The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).<sup>5-7</sup>

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).<sup>13</sup>

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.<sup>6</sup>

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.<sup>7</sup> Results at week 24 of the study.

|| The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).<sup>8,9</sup>

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).<sup>8,13</sup>

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).<sup>9</sup>